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Pathogenesis and Treatment of Macrocytic Anemia
Patricia A. McIntyre, Marie V. Sachs, Julius R. Krevans, and C. Lockard Conley

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Abnormal Forms of Hemoglobin from a Genetic Point of View
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Blood Disorders Caused by Drug Sensitivity
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Newer Agents in the Treatment of Leukemia
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Hexosamine Excretion in Urine During Pregnancy
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Medical Management of Adrenalectomy and Hypophysectomy
M. B. Lipsett, M. C. Li, and O. H. Pearson

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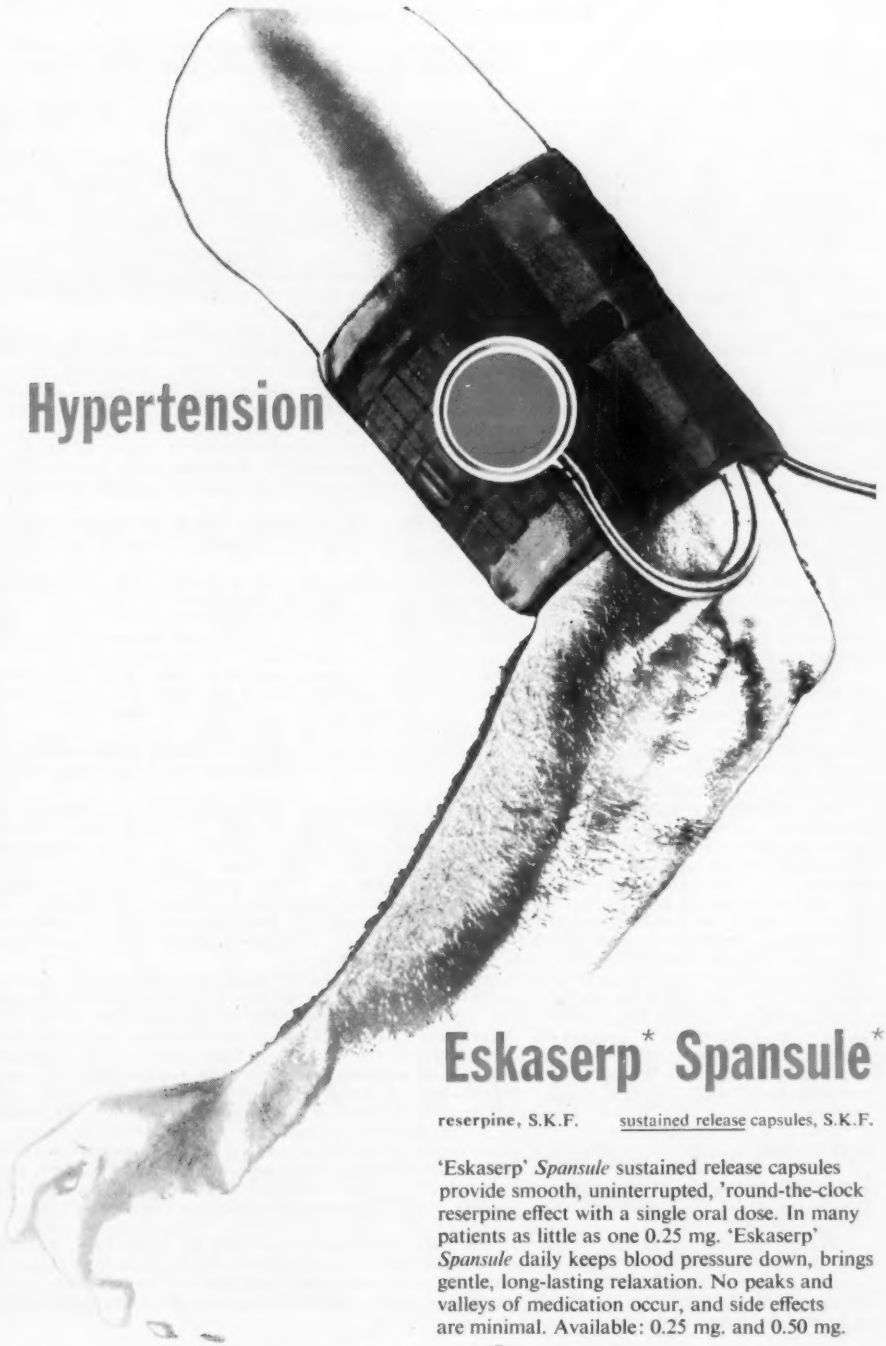

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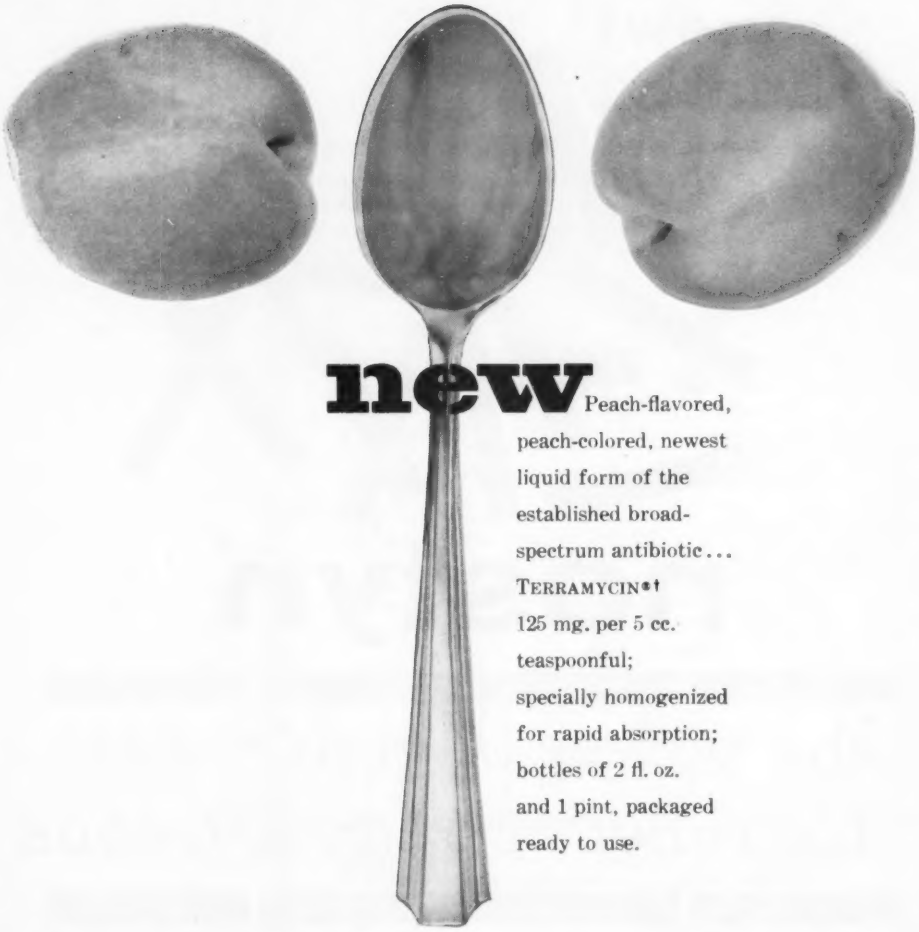

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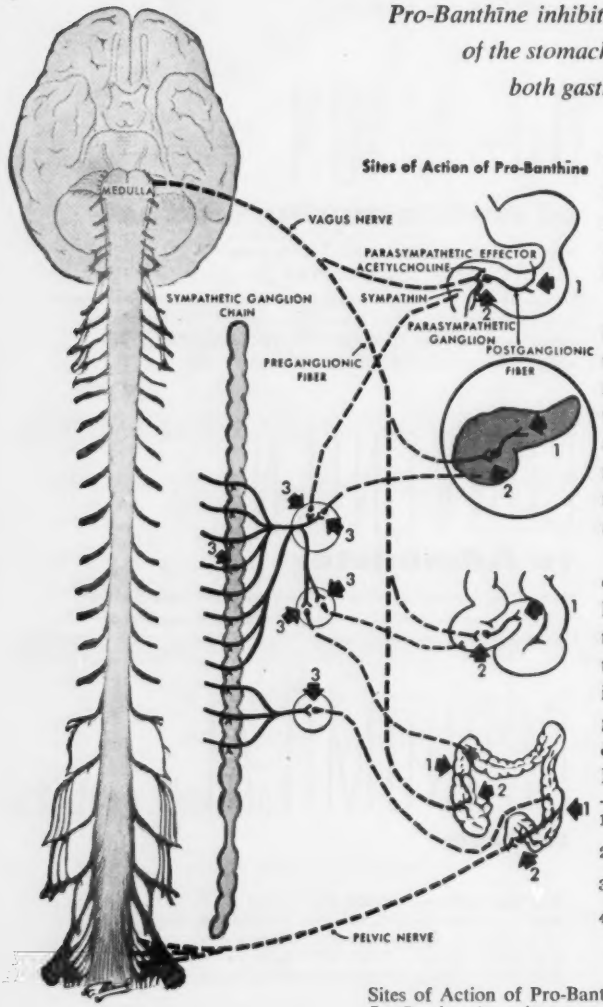

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1. Jones, C. A.: Arch. Int. Med. *96*:332 (Sept.) 1955.
2. Zollinger, R. M.: Postgrad. Med. *15*: 323 (April) 1954.
3. Woodward, E. R.: M. Clin. North America *38*:115 (Jan.) 1954.
4. Schwartz, I. R., and Hinton, J. W.: Personal communication, February, 1955.

SEARLE

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Hematology

Pathogenesis and Treatment of Macrocytic Anemia

Information Obtained with Radioactive Vitamin B_{12}

PATRICIA A. McINTYRE, M.D.
MARIE V. SACHS, A.B.
JULIUS R. KREVANS, M.D.
and
C. LOCKARD CONLEY, M.D., Baltimore

The clinical manifestations of pernicious anemia are believed to be wholly attributable to a deficiency of vitamin B_{12}. This deficiency is not the result of improper diet but is caused by impaired absorption of the vitamin from the gastrointestinal tract. For vitamin B_{12} to be absorbed in adequate amounts, a substance present in the secretion of the normal stomach is required. This substance, the intrinsic factor of Castle, has not yet been identified or obtained in pure form. The mode of action of intrinsic factor is unknown, but virtually all evidence indicates that it simply facilitates the absorption of vitamin B_{12}. The basic defect in pernicious anemia is an abnormality of the stomach which fails to produce intrinsic factor. As a result vitamin B_{12} is not absorbed even though ingested in usual amounts. Similar deficiency states are encountered with certain other disorders of the alimentary canal in which there is impaired absorption of the vitamin, but clinical manifestations attributable solely to inadequate dietary intake are extremely rare.

These considerations make apparent the importance of methods for measuring directly the absorption of vitamin B_{12} from the gastrointestinal tract. By the time that vitamin B_{12} became available, a microbiological method was at hand for its detection and measurement. We attempted to use microbiological methods in our first efforts to measure the rate of absorption and utilization of the vitamin.[1] When as little as 25γ was injected parenterally, a small fraction appeared in the urine of normal subjects and of patients with pernicious anemia in relapse. No difference could be detected between the normal subjects and the patients in this study. When larger amounts of the vitamin were injected, increasingly greater proportions were promptly excreted. The injection of 500γ or more was followed by

Submitted for publication June 1, 1956.

Clinical Fellow of the American Cancer Society (Dr. McIntyre).

From the Department of Medicine, The Johns Hopkins University and Hospital.

This work was carried out under Contract AT (30-1) 1208 between the Atomic Energy Commission and The Johns Hopkins University. The vitamin B_{12} used in these studies was generously provided by Merck & Co., Inc. The intrinsic factor concentrate was kindly supplied by Organon, Inc.

Read in the Symposium on Hematology of the Joint meeting of the Section on Experimental Medicine and Therapeutics and the Section on Internal Medicine at the 105th Annual Meeting of the American Medical Association, Chicago, June 14, 1956.

virtually complete recovery of the vitamin in the urine within several hours.

It was anticipated that oral administration of a large amount of vitamin B_{12} to normal persons would result in its absorption and subsequent appearance in the urine. In contrast, we thought, patients with pernicious anemia would fail to absorb the vitamin. Thus, we hoped to measure directly the absorptive capacity of the intestine by assays of urine after an oral dose. The results of this study were completely disappointing. When as much as 10,000γ of vitamin B_{12} was given orally to normal subjects, no increase in urinary excretion could be detected. This was the first evidence that absorption of vitamin B_{12} by normal persons is restricted.

In 1950, Chaiet, Rosenblum, and Woodbury [2] produced labelled vitamin B_{12} by adding radioactive cobalt to the medium in which the vitamin was synthesized by microorganisms. Our first studies with radioactive vitamin B_{12} were designed to measure quantitatively the amount absorbed from the intestinal tract of normal subjects and patients with pernicious anemia. When 5γ of the labelled vitamin was administered orally, more than 80% of the radioactivity was recovered in the feces, indicating that very little was absorbed even by normal persons.[3] Subsequently, Heinle and his associates [4] found that if only 0.5γ of the labelled vitamin was administered, most of the radioactivity was absorbed by normal subjects. However, in patients with pernicious anemia, most of the radioactivity was excreted in the feces. Later studies * demonstrated the important relationship between the size of the oral dose of vitamin B_{12} and the fraction which is absorbed (Fig. 1). When the oral dose is 0.5γ or less, normal persons absorb more than 50%. Even when the dose is reduced to 0.1γ, however, an appreciable fraction appears in the stools.

* References 5 and 6.

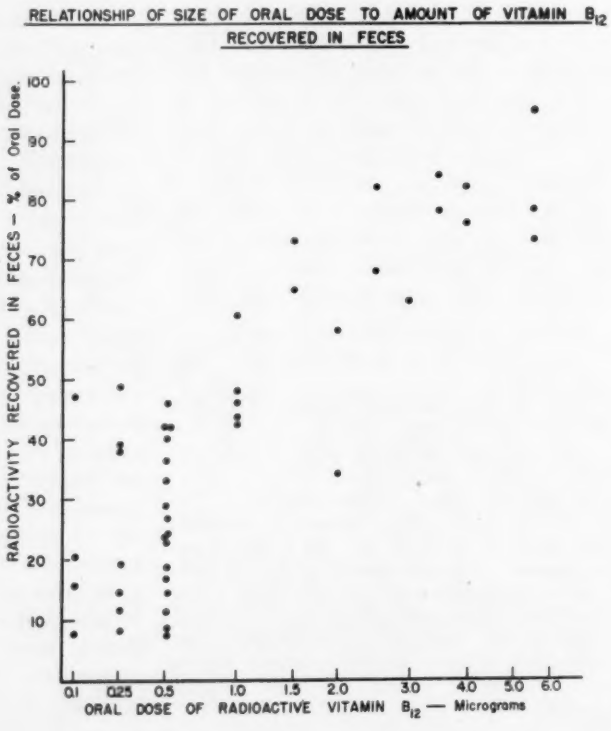

Fig. 1.—The results of 47 tests on 17 subjects with normal absorption of vitamin B_{12} are tabulated. The data were obtained from the published reports of two groups of investigators (References 5 and 6).

When the oral dose is increased above 0.5γ, such a large fraction may be unabsorbed that normal persons cannot be distinguished from patients with pernicious anemia by this technique.

The amount of vitamin B_{12} which can be absorbed by normal persons seems to be little more than the estimated requirement. Why the absorption should be so restricted is not apparent. Vitamin B_{12} is nontoxic, even when administered intravenously in extremely large amounts, and excessive quantities are rapidly disposed of in the urine. The absorption of the vitamin by normal subjects is not determined by the supply of intrinsic factor, since administration of potent intrinsic-factor concentrate does not increase the uptake.[7]

Measurement of the residual radioactivity of the feces after an appropriately small oral dose of labelled vitamin B_{12} has proved to be an effective and reliable method for detecting impaired absorption of the vitamin. The stools must be collected *in toto* until radioactivity is no longer present, a period of at least six days. Patients with pernicious anemia regularly show decreased absorption, so that a high percentage of the administered radioactivity is recovered in the stools. Patients with total gastrectomy or with certain disorders of the small intestine may also show marked impairment of absorption.

Schilling[8] demonstrated that the parenteral injection of a large amount of nonradioactive vitamin B_{12} could "flush" out into the urine a portion of the radioactivity absorbed from a previously administered oral dose of labelled vitamin. In his procedure one measures the radioactive vitamin B_{12} which has been absorbed and excreted in the urine, rather than that which is recovered in the feces. Schilling originally proposed that an oral dose of 2γ of the labelled vitamin be used. However, a significantly larger fraction of the administered dose is recovered in the urine if the oral dose is reduced to 0.5γ. Apart from simplicity and speed, the Schilling technique has another unique advantage which has permitted its use as a measure of rate as well as extent of vitamin B_{12} absorption.

When 0.5γ of radioactive vitamin B_{12} is given orally to normal fasting subjects and

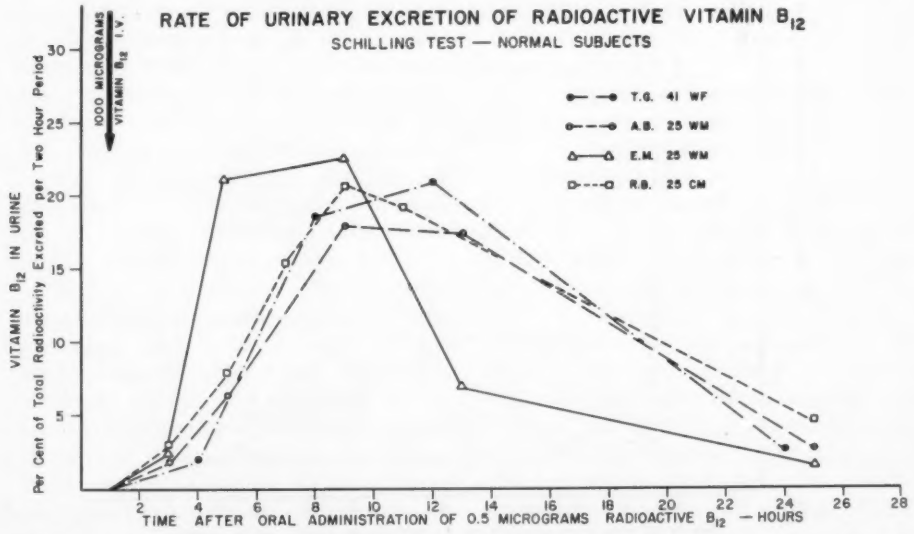

Fig. 2.—In this study urine was collected at two-hour intervals and the radioactivity of each specimen determined. No measurable radioactivity appeared in the urine before the injection of 1000γ of nonradioactive vitamin B_{12} was given. Appreciable activity was detected at 5 hours, but the peak excretion of radioactivity was not reached until 8 to 12 hours after the oral dose.

followed in one hour by the intravenous injection of 1000γ of nonradioactive vitamin B_{12}, approximately 25% of the orally administered radioactivity appears in the urine within 24 hours. This represents about one-third of the total radioactivity which has been absorbed.† Figure 2 shows the time pattern of the urinary excretion of radioactivity in four normal subjects. To be noted is the delay of about 5 hours before the initial appearance of radioactivity and the peak excretion 8 to 12 hours after the oral dose. In contrast, parenterally administered vitamin B_{12} appears promptly in the urine, excretion being virtually complete within two or three hours.[1] Simultaneous measurement of excretion of the nonradioactive vitamin B_{12} by microbiological assay ‡ and of the urinary radioactivity shows that the peaks do not coincide (Fig. 3). It is obvious that the radioactive vitamin B_{12} is not carried out on the crest of the flood of the parenterally administered vitamin. The effect of varying the time and amount of the parenteral injection was studied in four normal subjects (Fig. 4). Whether the parenteral dose was given as a single intravenous injection of 1000γ one hour or five hours after the oral dose or as a continuous infusion of 4500γ over a period of seven hours, the pattern and extent of urinary excretion of radioactivity were the same, except that no radioactivity appeared in the urine until after the injection was given. On the other hand, if the in-

† References 5 and 9.

‡ The microbiological assays were performed in the laboratory of Dr. B. F. Chow, who assisted in this study.

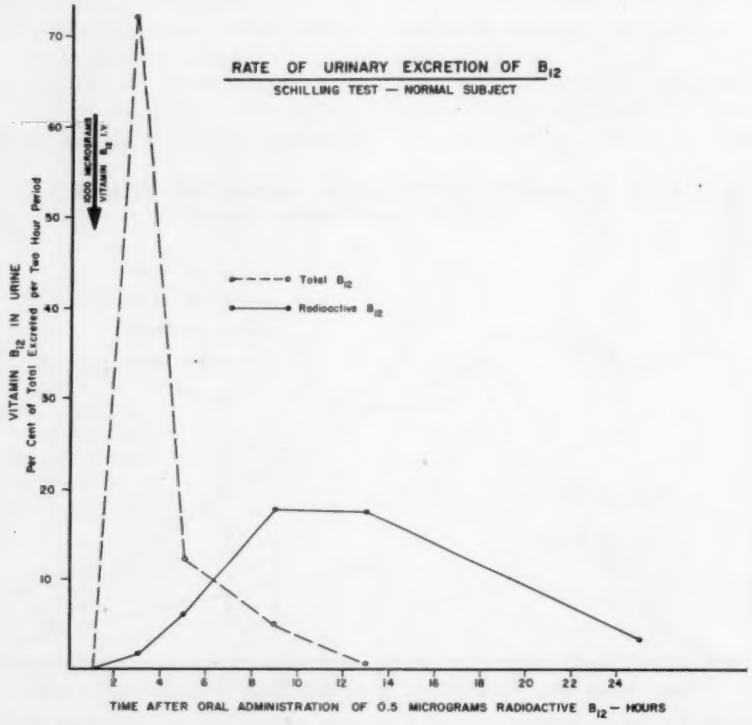

Fig. 3.—Following the intravenous injection of 1000γ of vitamin B_{12}, urinary excretion of the injected vitamin was prompt. In contrast, excretion of the radioactivity of the previously administered oral dose was much delayed.

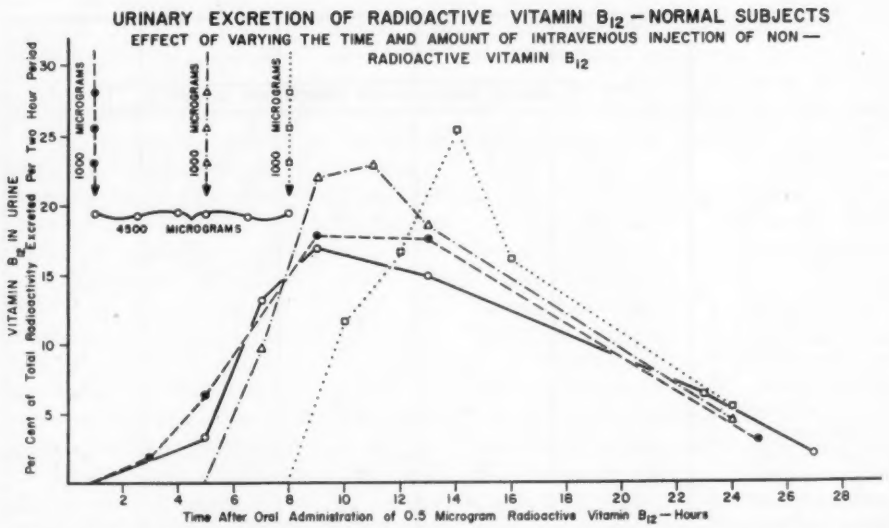
URINARY EXCRETION OF RADIOACTIVE VITAMIN B12 — NORMAL SUBJECTS
EFFECT OF VARYING THE TIME AND AMOUNT OF INTRAVENOUS INJECTION OF NON—RADIOACTIVE VITAMIN B12
1000 MICROGRAMS
1000 MICROGRAMS
1000 MICROGRAMS
4500 MICROGRAMS
VITAMIN B12 IN URINE
Per Cent of Total Radioactivity Excreted Per Two Hour Period
Time After Oral Administration of 0.5 Microgram Radioactive Vitamin B12 — Hours

Fig. 4.—The results of this study demonstrate that none of the orally administered radioactivity appeared in the urine until the parenteral injection of vitamin B_{12} was given. However, when the injection was given as long as five hours after the oral dose, there was no alteration in the peak of excretion of radioactivity. When the injection was given eight hours after the oral dose, not only the appearance of radioactivity but also the peak excretion was delayed. The total amount of radioactivity recovered was essentially the same in all of these subjects. Three subjects received single intravenous injections of 1000γ of vitamin B_{12}, as indicated by the arrows; the fourth was given 4500γ by continuous intravenous infusion for seven hours, as indicated by the bracket.

jection was delayed until eight hours after the oral dose, the urinary excretion of radioactivity was delayed. These observations suggest that the long lag between the time of oral administration of the labelled vitamin and its appearance in the urine represents largely the transit time through the alimentary canal and the intestinal mucosa. This view is supported by the recent observation of Doscherholmen and Hagen,[10] who found that peak radioactivity in blood was not achieved until 8 to 12 hours after an oral dose of labelled vitamin B_{12}.

The Schilling test has now become a routine procedure in many hospital laboratories and has proved to be an important and reliable diagnostic test. Two points concerning its use should be emphasized: 1. The result is significantly influenced by the size of the oral dose of labelled vitamin B_{12}, which should be rigidly standardized in micrograms rather than in microcuries. We prefer the 0.5γ oral dose. No extraneous source of vitamin B_{12} should be ingested in temporal relationship to the test procedure. 2. The test may be invalid in the presence of renal insufficiency. Our results as well as those of others § show that the renal excretion of vitamin B_{12} may be retarded and diminished in the presence of renal disease.

The results of some of our experience with the modified Schilling procedure are shown in Figure 5. With the 0.5γ oral dose, the radioactivity recovered in the urine of 15 normal adults ranged between 13.9% and 36.0% of that administered. A group of patients with disorders unrelated to pernicious anemia and without recognized intestinal or renal disease included some who excreted somewhat less radioactivity than the normal subjects. Similarly, in a group of persons with achlorhydria after the injection of histamine, some showed definitely subnormal absorption although none had evidences of pernicious anemia.

The greatest virtue of the test is the ability to detect pernicious anemia even in

§ Rath, C.: Personal communication to the authors. Reference 11.

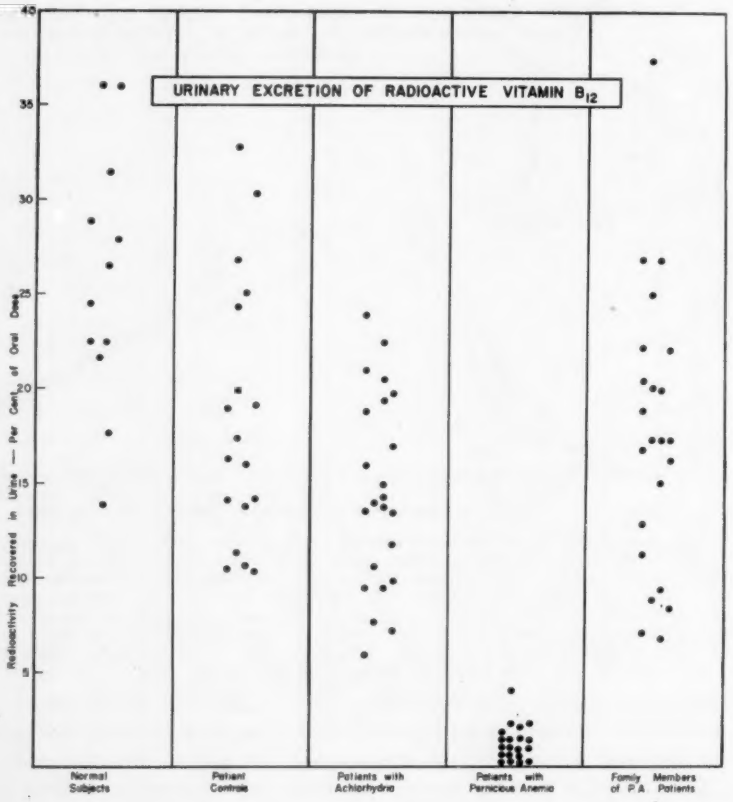

Fig. 5. — Results of modified Schilling tests in 96 persons are shown. In these tests an injection of 1000γ of nonradioactive vitamin B_{12} was given intravenously one hour after the oral dose of 0.5γ of labelled vitamin B_{12} to the fasting subject. The radioactivity recovered in urine collected for 24 hours is expressed as per cent of the orally administered radioactivity. The normal subjects were healthy persons between the ages of 20 and 41.

patients who are in complete remission as a result of prior therapy. The ill-advised but widespread use of multivitamin and multihematinic preparations containing folic acid and vitamin B_{12} has made this a diagnostic problem of major importance.[12] Many patients with pernicious anemia receive some form of therapy before the diagnosis is established. After remission has been induced in this manner, diagnosis may be impossible except by use of the radioactive tracer test. Twenty-two patients with typical pernicious anemia excreted between 0.2% and 4.1% of the radioactivity of the 0.5γ oral dose.

A constitutional predisposition to pernicious anemia and occasional familial occurrence of the disease are well known.[13] It seems likely that the gastric atrophy which gives rise to the clinical disease may be an inherited disorder. The occurrence of achlorhydria in some apparently healthy members of the families of pernicious anemia patients has been observed and supports this concept.[14] Furthermore, some patients with pernicious anemia have fortuitously been noted to have achlorhydria years before evidences of the anemia appeared. Therefore, a group of siblings and children of patients with pernicious anemia were examined by the radioactive tracer technique. In the group of 23 healthy family members studied, 7 gave results of the urinary excretion test which were below the lower level of the normal control group. These observations are given greater significance by the fact that five of these seven persons were under the age of 40, and one with a test result of only 8.4% was a 12-year-old boy. At least one of those with

reduced vitamin B_{12} absorption had free hydrochloric acid in the gastric secretion, but three others were demonstrated to have achlorhydria after the injection of histamine.

The absorption defect in pernicious anemia is readily overcome by administering intrinsic factor concentrate with the oral dose of labelled vitamin B_{12}.[4] In patients with total gastrectomy, absorption of vitamin B_{12} is similarly impaired and also corrected by intrinsic factor.[15] Thus, the stomach itself is not necessary for absorption of the vitamin, provided that a source of intrinsic factor is present. In one of our studies radioactive vitamin B_{12} was introduced into the jejunum of two patients through feeding jejunostomy tubes. Although no supplementary intrinsic factor was given, absorption in the near-normal range occurred, indicating that absorption of the vitamin takes place below the upper 2 ft. of the terminal ileum. It is suggested therefore that a major site of vitamin B_{12} absorption is the lower small intestine. When the radioactive vitamin was instilled into the rectum, no detectible absorption occurred.

In sprue, a disease characterized by multiple absorption defects, there is usually profound impairment of vitamin B_{12} uptake. In this condition as well as in other disorders of the intestine, the absorption defect cannot be corrected by the administration of intrinsic factor.[16] Of considerable interest to us has been the discovery that pancreatic insufficiency may also be associated with impaired absorption of vitamin B_{12}. Four of the five patients studied have shown significantly reduced vitamin B_{12} uptake as measured by the Schilling procedure (Table 1). The defect in these cases was not corrected by intrinsic factor concentrate, by

TABLE 1.—*Results of Schilling Tests in Five Cases of Pancreatic Insufficiency*

Case	Age, yr.	Race	Sex	Diagnosis	Results of Schilling Test, Urinary Radioactivity Expressed as per Cent of Oral Dose			
					0.5 γ Co^{60} B_{12}	0.5 γ Co^{60} B_{12} + Intrinsic Factor Concentrate	0.5 γ Co^{60} B_{12} after Oxytetracycline, 1 Gm. Daily for 7 Days	0.5 γ Co^{60} B_{12} + Pancreatin, 1.54 Gm. Panteric Granules (Parke, Davis & Company)
1	37	W	M	Pancreatectomy subtotal gastrectomy, duodenectomy for chronic pancreatitis	1.9			
2	6	W	F	Cystic fibrosis of pancreas	9.3			
3	56	W	M	Idiopathic pancreatic insufficiency	4.9	2.7	4.9	
4	54	W	M	Chronic relapsing pancreatitis	8.2	1.9		3.3
5	69	W	F	Total pancreatectomy for carcinoma of pancreas	16.1			

intestine. Study of two patients who had had resection of all of the small intestine except for about 1 ft. of jejunum revealed that in both absorption of vitamin B_{12} was severely impaired. Thus it appears that little absorption of the vitamin takes place in the upper gastrointestinal tract. Three patients with regional enteritis have also demonstrated impaired absorption. In one of these the disease appeared to involve only about

antibiotics, or by pancreatin. Since normal absorption was observed in one patient after total pancreatectomy, it seems unlikely that the secretions of the pancreas per se are required for the absorption of vitamin B_{12}.

Certain parasitic organisms inhabiting the intestinal tract successfully compete with their host for the available vitamin B_{12}, thus inducing a deficiency state. This seems clearly to be the pathogenesis of the perni-

cious-anemia-like syndrome occurring in some persons harboring the fish tapeworm.[17] Diverticula and other blind-loop lesions of the small intestine may contain bacterial organisms which utilize the vitamin. There is good evidence that the megaloblastic anemia which occasionally is associated with such lesions is the result of this bacterial competition. Eradication of the infecting organisms by the administration of appropriate chemotherapeutic agents has been demonstrated to overcome the apparent absorption defect in these cases.||

Summary

Clinical vitamin B_{12} deficiency states are almost always the result of impaired absorption of the vitamin from the gastrointestinal tract. The use of vitamin B_{12} labelled with radioactive cobalt has made possible direct measurement of the capacity of the intestine to absorb the vitamin. A surprising result has been the demonstration of the limited and retarded absorption of vitamin B_{12} by normal persons. Severely impaired uptake of the vitamin is regularly encountered in patients with pernicious anemia. Family members of patients with pernicious anemia not infrequently are found to have subnormal absorption. Defective absorption occurring as a result of deficiency of intrinsic factor can be corrected by administration of a source of intrinsic factor together with vitamin B_{12}. Absorption defects are not overcome by intrinsic factor concentrate when they result from functional or anatomical derangements of the small intestine, as in sprue, enteritis, pancreatic insufficiency, and intestinal resection. When deficient absorption is the result of utilization of the vitamin by parasitic organisms in the intestinal tract, destruction of the organisms corrects the defect. The restricted absorption of vitamin B_{12} from the alimentary canal, even in normal persons, makes it obvious that intensive therapy with the vitamin can be effectively accomplished only by parenteral administration.

|| References 18 and 19.

ABSTRACT OF DISCUSSION

FRANK H. BETHELL, M.D., Ann Arbor, Mich.: Methods employing radioactive vitamin B_{12} provide, first, precise criteria for establishing the presence or absence of Addisonian pernicious anemia, even in patients who have been receiving therapy and whose blood values are normal; second, such tests are of great value in differentiating the several forms of vitamin-B_{12}-deficiency anemia

TABLE 2.—*Schilling Tests in Cases of Megaloblastic Anemia Other than in Pernicious Anemia and After Gastrectomy*

Case	Age, yr.	Race	Sex	Diagnosis	Co^{60} B_{12}, γ	Per Cent Radioactivity Recovered*		
						B_{12} Only	B_{12} + Intrinsic Factor	B_{12} Only
1	68	W	M	Dietary defic.	2.3	11.5 (+)		After 5 days of chlortetracycline (Aureomycin) adm.
2	73	W	M	Dietary defic. (1)	1.0	23.8 (+)		
				(2)	1.0	25.8 (+)		
3	20	W	M	Blind loop of ileum (44 days after surgical correction)	1.0	0.1 (−)	0.3 (−)	7.4 (+)
					1.0	2.8 (±)		
4	41	W	F	Ileectomy	1.0	0.2 (−)	0.5 (−)	0.3 (−)
5	21	W	M	Tb. enterocolitis	1.0	1.1 (−)	1.4 (−)	
6	20	W	M†	Juvenile P.A.	1.0	0.3 (−)	14.8 (+)	
7	61	W	F‡	Diphenylhydantoin therapy (1)	2.2	14.5 (+)	19.5 (+)	
				(2)	2.2	21.3 (+)		

* + or − indicates interpretation of result.
† The patient was seen with megaloblastic anemia at age of 6 mo. Gastric analysis at age 20 yr. showed normal volume, acidity, and pepsin. Schilling test with patient's gastric juice gave negative result for intrinsic factor activity.
‡ Megaloblastic anemia occurring after prolonged therapy with antiepileptics of the diphenylhydantoin (Dilantin) type is believed to result from interference with folic acid metabolism.

to which Dr. Conley has referred as well as in aiding to distinguish between lack of B_{12} and folic acid as a cause of megaloblastic anemia.

Were it not for the fact that certain reservations exist among some physicians relative to the use, for diagnostic purposes, of even minute amounts of radioactive isotopes, especially those with long radiation half-lives, it could be justifiably maintained that a radioactive vitamin B_{12} absorption or excretion test is a present-day requirement for the diagnosis of pernicious anemia. No injurious effects from the radiation involved have been reported, and most clinicians and health physicists regard the procedures as entirely innocuous when done within the prescribed limitations.

Dr. Conley has emphasized the application of the urinary excretion test, or Schilling test, to the study of the absorption defect in Addisonian pernicious anemia. I should like to amplify his comments on other vitamin-B_{12}-deficiency states manifested by macrocytic anemia and megaloblastic bone marrow.

In addition to pernicious anema, the pathogenesis of B_{12} deficiency may be elucidated by means of the Schilling test in cases of megaloblastic anemia due to abnormal diet and those caused by anatomic and functional disorders of the gastrointestinal tract (Table 2). Worthy of mention, although rare, is the so-called juvenile pernicious anemia in which there may be a congenital selective lack of intrinsic factor in the gastric juice without achlorhydria or other secretory abnormality.

REFERENCES

1. Conley, C. L.; Krevans, J. R.; Chow, B. F.; Barrows, C., and Lang, C. A.: Observations on the Absorption, Utilization, and Excretion of Vitamin B_{12}, J. Lab. & Clin. Med. 38:84, 1951.

2. Chaiet, L.; Rosenblum, C., and Woodbury, D. T.: Biosynthesis of Radioactive Vitamin B_{12} Containing Cobalt^{60}, Science 111:601, 1950.

3. Krevans, J. R.; Conley, C. L., and Barrows, C. R., Jr.: Observations on the Absorption and Excretion of Vitamin B_{12}, Bull. Johns Hopkins Hosp. 88:568, 1951.

4. Heinle, R. W.; Welch, A. D.; Scharf, V.; Meacham, G. C., and Prusoff, W. H.: Studies of Excretion (and Absorption) of C^{60}-Labelled Vitamin B_{12} in Pernicious Anemia, Tr. A. Am. Physicians. 65:214, 1952.

5. Krevans, J. R.; Conley, C. L., and Sachs, M. V.: Radioactive Tracer Tests for the Recognition and Identification of Vitamin B_{12} Deficiency States, J. Chron. Dis. 3:234, 1956.

6. Callender, S. T., and Evans, J. R.: Observations on the Relationship of Intrinsic Factor to the Absorption of Labelled Vitamin B_{12} from the Intestine, Clin. Sc. 14:387, 1955.

7. Swendseid, M. E.; Gasster, M., and Halsted, J. A.: Limits of Absorption of Orally Administered Vitamin B_{12}: Effect of Intrinsic Factor Sources, Proc. Soc. Exper. Biol. & Med. 86:834, 1954.

8. Schilling, R. F.: Intrinsic Factor Studies: II. The Effect of Gastric Juice on the Urinary Excretion of Radioactivity After the Oral Administration of Radioactive Vitamin B_{12}, J. Lab. & Clin. Med. 42:860, 1953.

9. Callender, S. T., and Evans, J. R.: The Urinary Excretion of Labelled Vitamin B_{12}, Clin. Sc. 14:295, 1955.

10. Doscherholmen, A., and Hagen, P. S.: Radioactive Vitamin B_{12} Absorption Studies: Results of Direct Measurement of Radioactivity in the Blood, J. Clin. Invest. 35:699, 1956.

11. Bull, F. E.; Campbell, D. C., and Owen, C. A., Jr.: Evaluation of Intrinsic Factor in Pernicious Anemia by Means of Cobalt^{60}-Vitamin B_{12}. Fed. Proc. 15:509, 1956.

12. Conley, C. L., and Krevans, J. R.: New Developments in the Diagnosis and Treatment of Pernicious Anemia, Ann. Int. Med. 43:758, 1955.

13. Maclachlan, W. W. G., and Kline, F. M.: Occurrence of Anemia in 4 Generations, Am. J. M. Sc. 172:533, 1926.

14. Conner, H. M.: Hereditary Aspects of Achlorhydria in Pernicious Anemia: A Study of Gastric Acidity in 154 Relatives of 109 Patients Having Pernicious Anemia, J. A. M. A. 94:606, 1930.

15. Swendseid, M. E.; Halsted, J. A., and Libby, R. L.: Excretion of Cobalt^{60}-Labelled Vitamin B_{12} After Total Gastrectomy, Proc. Soc. Exp. Biol. & Med. 83:226, 1953.

16. Jerzy Glass, G. B.: The Role of the Gastro-Intestinal Tract in the Pathogenesis and Management of Pernicious Anemia, Bull. New York M. Coll. 16:1, 1953.

17. von Bonsdorff, B.: Pernicious Anemia Caused by Diphyllobothrium Latum, in Light of Recent Investigations, Blood 3:91, 1948.

18. Krevans, J. R.; Conley, C. L., and Sachs, M. V.: Influence of Certain Diseases on the Absorption of Vitamin B_{12} From the Gastrointestinal Tract, J. Clin. Invest. 33:949, 1954.

19. Halsted, J. A.; Lewis, P. M., and Gasster, M.: Absorption of Radioactive Vitamin B_{12} in the Syndrome of Megaloblastic Anemia Associated with Intestinal Stricture or Anastomosis, Am. J. Med. 20:42, 1956.

The Mechanism and Treatment of Iron-Deficiency Anemia

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Iron-deficiency anemia occurs at all ages, but its pathogenesis is different in childhood and adult life. Excretion of iron is negligible. In the growing child, the needs of an expanding red cell mass require appreciable absorption of dietary iron, and the anemic child will usually be found to have a diet insufficient in iron-containing foods. In adult life, a constant amount of iron is present in the red cell mass, and an additional supply, available for hemoglobin production if needed, is stored in the tissues. Once iron stores are accrued, the adult is virtually independent of dietary iron, and iron deficiency develops only after chronic blood loss.

Pathogenesis

Iron balance during the first year is diagramed in Figure 1. An average newborn infant has a blood volume of 250 ml., of which 150 ml. represents red cells.[1] In the first year, the blood volume increases to 750 ml., and in order to achieve a normal hematocrit of 40%, the child must absorb 150 mg. of iron from dietary sources, such as meat and enriched cereals. On the other hand, if the diet consists exclusively of milk, the child absorbs no iron and cannot expand his red cell mass. The increasing total blood volume results in a fall in the hematocrit to 20%, representing a severe iron-deficiency anemia. Blood loss does not enter the picture in the typical iron-deficiency anemia in infancy.

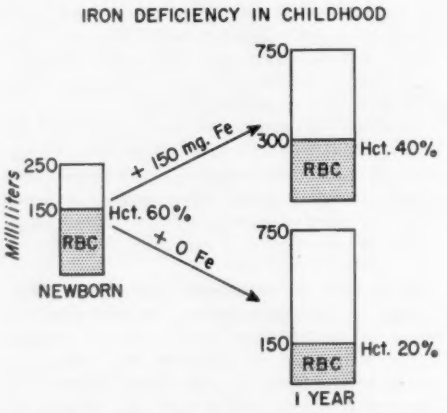

Fig. 1.—Total blood volume and red cell mass are indicated in milliliters, at birth and one year, for child on normal diet (upper arrow) and on exclusively milk diet (lower arrow). One milliliter of red cell mass contains approximately 1 mg. Fe, and so the normal child, having no iron stores, must absorb 150 mg. Fe from the diet. Since a milk diet is essentially iron-free, it permits no iron absorption and leads to iron-deficiency anemia (Blood volume figures based on data of Mollison and co-workers.[1])

In the adult, the red cell mass contains approximately 2500 mg. of iron (Fig. 2). There is an iron store of about 1500 mg. in the form of ferritin and hemosiderin which has been accumulated during the first 20 years of life.[2] There is a smaller amount, estimated at 500 mg. or less, in the form of tissue enzymes and myoglobin, and a very small compartment, approximately 3 mg., in the plasma, representing transport iron. In the nonbleeding person, both iron absorption and excretion are low. Iron from destroyed red cells is reutilized repeat-

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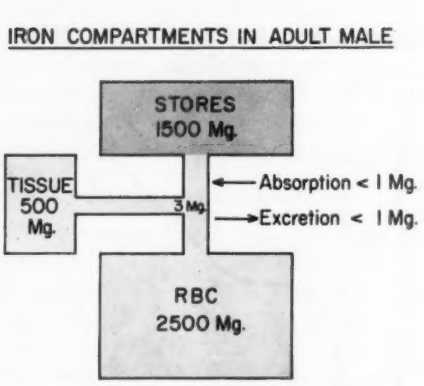

Fig. 2.—The healthy adult male has 4.5 gm. of total body iron, of which 2500 mg. is present in the red cell mass, the same iron being utilized repeatedly for hemoglobin production; 1500 mg. is present in liver and reticuloendothelial organs as ferritin and hemosiderin, all available for hemoglobin production if needed; 500 mg. is contained in cytochrome enzyme systems and myoglobin and is unavailable for hemoglobin production; 3 mg. circulates in plasma attached to the iron-binding protein and functions as transport iron. There is minimal daily exchange between body iron and the environment.

edly for new hemoglobin production.

As blood loss occurs, the bone marrow utilizes existing iron stores to manufacture new hemoglobin for replacement of that lost, and therefore storage iron is the adult's buffer against the development of iron-deficiency anemia. Once depleted, iron stores are reconstituted so slowly that the chronic or recurrent bleeder easily develops iron-deficiency anemia. Since dietary iron absorption is often inadequate to permit restoration of the red cell mass, the anemia may be a lifetime disease (Fig. 3). Iron loss through menstruation and multiple pregnancies explains the much higher incidence of iron-deficiency anemia in females in and beyond the menstrual age.

When the iron stores are exhausted, the plasma iron falls, erythropoiesis is decreased, and finally anemia develops and the first symptoms appear, months after onset of excess bleeding. The anemia is at first normocytic, but with impairment in hemoglobin synthesis, new red cells become hypochromic and microcytic. After several years of an iron-deficiency state, epithelial changes appear, including spoon nails, a smooth sore tongue, sores at the corners of the mouth, and dysphagia caused by fibrous adhesions at the upper end of the esophagus.

Laboratory

The laboratory diagnosis of iron-deficiency anemia includes a group of nonspecific findings relating to sequential events of iron depletion. Since the first event is exhaustion of storage iron, the most sensitive index of iron deficiency has been inspection of an unstained smear of bone marrow for hemosiderin.[3] Hemosiderin is the visible form of iron stores, appearing as golden yellow refractile granules against the reticulum background of the marrow. The marrow of a normal person contains a small number of these granules. In iron-deficiency anemia, the granules are essentially absent. In anemias not due to iron deficiency, iron is not lost from the body but is shifted from the red cell mass into the stores, and bone marrow hemosiderin is increased. Although

TIME SEQUENCE	EVENTS
Chronic blood loss for	
SEVERAL MONTHS	DEPLETION OF IRON STORES
	DECREASE IN PLASMA IRON
after MORE MONTHS	ANEMIA, normocytic (at first)
	ANEMIA, red cells become microcytic and hypochromic
	DECREASE IN SERUM BILIRUBIN
after SEVERAL YEARS	EPITHELIAL CHANGES:
	spoon nails
	glossitis
	cheilosis
	dysphagia

Fig. 3.—Sequence of events in iron depletion.

quantitatively crude, this direct visualization of the iron stores enables one categorically to rule out iron deficiency if hemosiderin granules are normal or increased. On the other hand, if the hemosiderin is reduced or absent, then iron stores are reduced, but one cannot be certain that this is the only cause of anemia.

In iron-deficiency anemia, the plasma iron is low. The reticulocyte count and serum bilirubin are decreased, and the plasma gives a pale watery appearance. At first, the red cells on smear are normal, but later they become hypochromic and microcytic, as described above. There may be target cells and, particularly in infants, nucleated red cells. Although morphologic red cell changes are a late index of iron depletion, careful blood smear examination remains the most practical, simple laboratory test for the tentative diagnosis of iron-deficiency anemia.

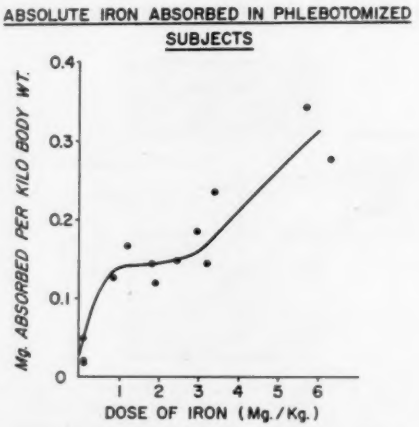

Fig. 4.—Relation of absolute iron absorbed to the dose. Healthy adult males were bled 15% of total blood volume in two phlebotomies and 10 days later were fed varying doses of ferrous iron salt, tagged with radioiron. A plateau in absolute iron absorbed was noted in dosage range 1 to 3 mg/kilogram of body weight, above which a further increase in absorption occurred.

Therapy—Oral Iron

The only certain diagnostic test for uncomplicated iron-deficiency anemia is response of the patient to iron therapy. It should be administered in the form of reduced iron salts, such as ferrous sulfate or gluconate. Absorption is to some extent a function of the amount of iron administered, as indicated by observations in subjects with blood loss anemia (Fig. 4).* However, a plateau in absorption is reached at 1 mg/kilogram of body weight, which is not materially increased until the dose is tripled. This dose, 60 mg. in an average person, coincides with the amount tolerated by most patients and is the amount of iron contained in one tablet of most ferrous salts.

Iron given in the fasting state is better absorbed, but produces more frequent symptoms of gastric intolerance. Therefore, it is recommended that one tablet of a ferrous salt be taken with meals, three times daily. An adequate response can be defined as a rise in hemoglobin of 2 gm. per 100 cc. within three weeks, and if the patient responds, treatment should be continued until the hemoglobin level is normal. Continued active bleeding will of course reduce or nullify the response. Continuation of oral iron therapy after correction of anemia is of little benefit, since absorption in the nonanemic person is so slight that reconstitution of depleted stores by the oral route would require many months or years.

Adjuvants to iron therapy are not necessary and not recommended. Hydrochloric acid is unnecessary, since it has been demonstrated that patients with gastric achlorhydria can absorb iron as well as normals. In tests employing radioactively tagged iron salts, the addition of ascorbic acid as a reducing substance had little effect on the amount absorbed.† Many other substances are added to iron in commercially available preparations which tend to confuse the diagnostic significance of the response of the patient to treatment. Since iron deficiency is often symptomatic of a serious bleeding disorder, it is important for the physician to confirm the diagnosis by knowing that his patient has responded to iron alone.

* Bothwell, T. H.: Unpublished data.

† Bothwell, T. H.: Unpublished data.

One preparation combines iron with cobalt. Since cobalt is known to result in a nonspecific rise in the red cell mass in both normal and anemic persons, it will obviously obscure the response of the patient to iron.

Therapy—Parenteral Iron

In recent years, satisfactory iron preparations for parenteral administration have become available. These are attended by significant local and systemic reactions and must be used with caution.[4] They are recommended in limited groups of patients (Fig. 5): those who cannot tolerate oral iron

INDICATIONS FOR PARENTERAL IRON

1. Intolerance of oral iron.
2. Inflammatory gastrointestinal disease.
3. Chronic bleeding lesion: need for creation of iron store.
4. Poor absorption of iron.

Figure 5

due to gastric symptoms; those who have inflammatory gastrointestinal disease, such as ulcerative colitis or regional enteritis, and patients who are chronic bleeders, such as those with familial telangiectasia with recurrent nosebleeds, in whom it is desirable to create iron stores. This can be done with certainty only by giving the iron parenterally. The inability to absorb iron usually indicates a widespread absorption defect, as in steatorrhea.

The parenteral preparation most extensively used in this country is saccharated oxide of iron, which must be administered intravenously and can be given in doses up to 200 mg. In the last two years, in reports from England, a new iron-dextran complex has been shown to be similarly effective in hemoglobin regeneration.[5] This substance can be given intramuscularly, is tolerated in doses up to 500 mg., and appears to be attended by a low incidence of local and systemic reactions. The preparation is now being tested in this country and may be available in a few months.‡

‡ Imferon, Lakeside Laboratories, Inc., Milwaukee.

If parenteral therapy is elected, it is recommended that initially only 500 mg. iron be given and the hemoglobin level followed for three weeks. If there is no response, one can be certain that iron deficiency is not the primary cause of the anemia, and further therapy with iron is not justified. If response occurs, one can calculate the patient's total replacement need by allowing 1 mg. of iron per milliliter deficit in red cell mass and adding 1500 mg. for replacement of the absent iron stores. In chronic or recurrent bleeders, larger stores may be built up as a reserve against future blood loss.

With the increased ease of parenteral administration of large amounts of iron there is danger of the production of iron storage disease by overloading the patient with iron. If a physician were to administer 40 doses of 500 mg. iron parenterally, he would bring his patient's total body iron into the range observed in clinical hemochromatosis.[6]

Summary

Iron-deficiency anemia is a disease of all ages. In children it is usually the result of a deficient diet, and treatment with iron should be supplemented by correction of the diet. In adults, iron-deficiency anemia is a symptom of chronic blood loss, and it may be the first signpost of a serious underlying bleeding lesion. Treatment is best given by mouth with reduced iron salts. Adjuvants to iron therapy are unnecessary and are not recommended, for they obscure the diagnostic significance of response to iron. Parenteral iron is indicated in certain patients. New preparations, especially iron-dextran, which may be administered in large doses intramuscularly, increase the ease and safety of parenteral therapy but at the same time raise the possible hazard of overloading the patient with iron.

REFERENCES

1. Mollison, P. L.; Veall, N., and Cutbush, M.: Red Cell and Plasma Volume in Newborn Infants, Arch. Dis. Childhood 25:242, 1950.

2. Haskins, D.; Stevens, A. R., Jr.; Finch, S. C., and Finch, C. A.: Iron Metabolism. Iron Stores in Man as Measured by Phlebotomy, J. Clin. Invest. 31:543, 1952.

3. Stevens, A. R., Jr.; Coleman, D. H., and Finch, C. A.: Iron Metabolism: Clinical Evaluation of Iron Stores, Ann. Int. Med. 38:199, 1953.

4. Coleman, D. H.; Stevens, A. R., Jr., and Finch, C. A.: The Treatment of Iron Deficiency Anemia, Blood 10:567, 1955.

5. Cappell, D. F.; Hutchison, H. E.; Hendry, E. B., and Conway, H.: A New Carbohydrate-Iron Haematinic for Intramuscular Use, Brit. M. J. 2:1255, 1954.

6. Finch, S. C., and Finch, C. A.: Idiopathic Hemochromatosis, an Iron Storage Disease; A. Iron Metabolism in Hemochromatosis, Medicine 34:381, 1955.

Abnormal Forms of Hemoglobin from a Genetic Point of View

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Accustomed as we all are by now to the rapid expansion of medical knowledge, nevertheless even the most phlegmatic among us cannot help but be impressed from time to time by occasional, truly explosive spurts in the usual orderly progression. Recent developments as regards the inherited abnormalities of human hemoglobin would seem to represent just such a spurt. Ten years ago hemoglobin, despite relatively intensive studies of its properties by the biochemist, appeared to be much the same from one person to the next. Today we recognize no less than nine different hemoglobin types, some of which, in specific parts of the world, contribute significantly to the total disease picture.

The first of the hematological entities associated with an abnormal hemoglobin, the sickling phenomenon, was actually recognized as long ago as 1910, by Herrick, although the fact that an abnormal form of hemoglobin was involved did not become clear until the work of Pauling and his associates, in 1949. Persons whose blood cells can be induced to sickle generally fall into two categories, exhibiting either the asymptomatic sickle-cell trait or a severe, chronic hemolytic anemia, known as sickle-cell anemia. In the United States, among Negro children, the ratio of persons with the trait to persons with the anemia is about 40:1, with the ratio higher among Negro adults because of the early death of persons with sickle-cell anemia.

The hereditary nature of the sickling phenomenon became apparent very shortly after the first recognition of sickle-cell disease. However, the genetic relationship between the sickle-cell trait and sickle-cell anemia has only become clear in recent years. As you are aware, the hereditary determiners, the genes, occur in pairs, one member of each pair derived from the male parent and the other from the female. The sickling phenomenon is due to the presence of an abnormal gene. When this gene is represented only once, i. e., in the heterozygous state, the result is the sickle-cell trait. When the gene is present in duplicate, i. e., is homozygous, sickle-cell anemia results. By and large, for the gene to be present in duplicate in a person, both of his parents must possess it. Hence, as a rule both parents of a person with true sickle-cell anemia will have the sickle-cell trait.

By the techniques of electrophoresis, it can readily be demonstrated that in persons with the sickle-cell trait, some 30% to 40% of the hemoglobin is of an abnormal type, whereas in persons with sickle-cell anemia, virtually all of the hemoglobin is abnormal. One of the most striking properties of this abnormal hemoglobin, termed Hemoglobin S, is its very low solubility when in the reduced state. It is only about 1/100 as soluble as normal hemoglobin. This low solubility is ultimately responsible for the sickling phenomenon, since when a sufficient amount of this hemoglobin becomes reduced

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either in vitro or, in persons with sickle-cell anemia, under the low oxygen tensions of venous blood, it tends, in effect, to "precipitate" within the erythrocyte. In this process the hemoglobin molecules align themselves in long chains, and here we have the basis of the red cell projections seen in the sickling phenomenon. These projections render the red cell more fragile, hence anemia; they also render the red cell less mobile, hence localized disturbances of circulation. This is a truly striking example of how a genetically controlled change in the structure of a protein molecule can set in motion a train of events resulting in severe disease.

The sickling phenomenon is encountered primarily in Negroes or persons of Negro descent, although it may occasionally be seen in Caucasians with no known Negro ancestry. One of the most striking examples of its occurrence in Caucasians involves certain villages in northern Greece, where 15%-30% of the inhabitants may exhibit the sickling trait. In some parts of Africa as many as 40% of the populace have the sickle-cell trait. Genetic theory enables us to predict that in these same areas as many as 3-4 infants per 100 should be expected to have sickle-cell anemia. In these same areas, infant mortality during the first year of life may run an appalling 500 per 1000 births. Small wonder that until recently we have heard relatively little of sickle-cell anemia in Africa; it has apparently been more or less lost in the great over-all death rates at the very early age levels. But where pediatric services are being organized in Africa the disease is being recognized with increasing frequency and, in fact, in the frequencies suggested by genetic theory. While making rounds with a Belgian pediatrician in the large government hospital in Leopoldville, Belgian Congo, last fall, I asked him to rank his medical problems in the order of their importance. First, of course, came the many infectious diseases, which are fast vanishing from the American scene and will likewise in the foreseeable future disappear from Africa, including such (to us) exotic entities as tetanus neonatorum. Then the parasitic diseases, also due to disappear. In a somewhat older age group, nutritional deficiencies, especially kwashiokor, are very important. And then, with no prompting on my part, he mentioned sickle-cell anemia, remarking on its chronicity, bringing the patient back time and again.

The second of the abnormal hemoglobins to be discovered, Hemoglobin C, came to light in the following manner. Two siblings were found to have an unusually mild form of sickle-cell anemia. Upon electrophoretic studies, their hemoglobin was found to be composed of a mixture of sickle-cell hemoglobin and a previously undescribed type. Family studies revealed that one parent had the sickle-cell trait. The other parent's red cells did not sickle but did possess the new abnormal hemoglobin, later called Hemoglobin C, in combination with normal hemoglobin, later designated Hemoglobin A. The presence of the abnormal hemoglobin seems to be determined by a single gene. In persons heterozygous for this gene, the Hemoglobin-C trait results. Persons with the trait sometimes show increased numbers of target cells. The target cell is a manifestation of an unusually thin erythrocyte, or leptocyte. Leptocytes have an increased resistance to hemolysis by hypotonic saline solutions, for which reason erythrocyte osmotic fragility is often less than normal in persons with the Hemoglobin-C trait. However, the Hemoglobin-C trait can be recognized with certainty only by the techniques of electrophoresis. In persons with the trait, 30% to 40% of the hemoglobin will be found to be of the abnormal type. Persons homozygous for the Hemoglobin-C gene exhibit somewhat more marked hematological abnormality. There are in stained blood films a striking number of target cells. There are evidences of moderately increased hemolysis—mild anemia, mild reticulocytosis. Splenomegaly is usually present.

In addition to sickle-cell hemoglobin and Hemoglobin C, we now recognize some seven other inherited hemoglobin abnormali-

ties. These have all come to light through subjecting to electrophoretic studies hemoglobin from persons with atypical or unusual hemolytic anemias, or else through survey studies of blood from selected groups. The survey studies are only practical because of the development of so-called filter-paper electrophoresis, in contrast to the more time-consuming and technically more difficult Tiselius electrophoresis. By convention, the hemoglobins are simply assigned the letters of the alphabet in the order of their discovery, unless, for clinical reasons, it seems preferable to assign a special letter, as in the case of Hemoglobin S, or sickle-cell hemoglobin.

Certain broad generalizations are beginning to emerge from the study of these hemoglobins, and it is to these that I wish to devote the remainder of this presentation.

(1) Firstly, with regard to the genetics of the situation. In general, heterozygosity with respect to any one of the genes responsible for an abnormal hemoglobin results in an asymptomatic carrier state, detectable only by such special tests as electrophoresis or the sickling test. In the carrier state, some 30%-40% of the hemoglobin is abnormal. In persons homozygous for the same gene, nearly 100% of the hemoglobin is abnormal.

(2) Secondly, with respect to the clinical hematology of the situation. By and large, there are no reliable criteria of the heterozygous or carrier state which can be applied to the ordinary stained blood film. With respect to homozygosity for the genes responsible for these hemoglobins, for only three—Hemoglobins S, C, and E—do we have sufficiently extensive studies to permit generalization. In each instance there is a striking increase in the number of target cells, so much so that the finding of greatly increased numbers of target cells, especially in a patient with a good nutritional history and no history of liver disease, should now automatically raise the question of the presence of an abnormal hemoglobin. In each case, there is an increased rate of hemolysis of the erythrocytes. The hemolytic disease is much more severe in persons homozygous for the Hemoglobin-S gene than in persons homozygous for either the C or E genes, this presumably due to the greatly decreased solubility of Hemoglobin S when reduced, as mentioned earlier.

(3) Thirdly, with respect to the racial distribution of the hemoglobins. For reasons which are not at all well understood at present, the genes responsible for the abnormal hemoglobins are very unequally distributed among the peoples of the earth. Thus, the Hemoglobin-S and -C genes are found primarily among Negroes, the Hemoglobin-E gene among Orientals. The practical corollary of this of course is that one's index of suspicion as to the occurrence of an abnormal hemoglobin should be particularly high when the hematological picture characterized above occurs in certain racial groups.

A word should be said at this point about the gene responsible for thalassemia, or Cooley's anemia. This gene, although widespread in distribution, is especially prevalent among persons living in the northeast sector of the Mediterranean basin, or their descendants. In heterozygotes, the gene produces thalassemia minor, or Cooley's trait, characterized by microcythemia with increased numbers of target and oval cells and, despite an apparent compensatory polycythemia, often a mild anemia. In homozygotes, the gene produces the severe, chronic, and ultimately fatal Cooley's anemia, or thalassemia major. The reason for mentioning the thalassemia gene at this point is simply that every so often through chance the thalassemia gene and the gene for one of the abnormal hemoglobins happen to occur in the same person. The result is usually a rather severe hemolytic anemia.

Due to chance, we may occasionally expect to encounter persons who possess as many as three different genes known to alter hemoglobin production. My colleagues, Drs. Schwartz, Spaet, Zuelzer, Robinson, and I have just finished the study of a family in which there occurs a person who almost certainly possesses the genes respon-

sible for thalassemia and Hemoglobins G and S, truly a "triple threat" man in any hematological backfield.

In conclusion, now, let me very briefly summarize the gist of my remarks as follows: The human hemoglobin types, readily detected by the technique of paper electrophoresis, are inherited as if due to single genes. In the heterozygous state, these genes result in asymptomatic carrier conditions. In the homozygous state, or in combination with a thalassemia gene, these genes result in anemias, to a large extent hemolytic in nature, of varying degrees of severity. On the basis of present knowledge, these anemias are especially apt to be encountered in persons of Negro or Oriental ancestry.

REFERENCES

1. Pauling, L.: Abnormality of Hemoglobin Molecules in Hereditary Hemolytic Anemia, Harvey Lect. 49:216-241, 1953-1954.

2. White, J. C., and Beaven, G. H.: A Review of the Varieties of Human Haemoglobin in Health and Disease, J. Clin. Path. 7:175-200, 1954.

3. Singer, K.: Hereditary Hemolytic Disorders Associated with Abnormal Hemoglobins, Am. J. Med. 18:633-652, 1955.

4. Chernoff, A. I.: Medical Progress: The Human Hemoglobins in Health and Disease, New England J. Med. 253:322-331, 365-374, and 416-423, 1955.

5. Itano, H. A.: Clinical States Associated with Alterations of the Hemoglobin Molecule: The Minot Lecture, A. M. A. Arch. Int. Med. 96:287-297, 1955.

6. Itano, H. A.: The Hemoglobins, Ann. Rev. Biochem., to be published.

7. Zuelzer, W. W.; Neel, J. V., and Robinson, A. R.: Abnormal Hemoglobins, in Progress in Hematology, edited by L. M. Tocantins, New York, Grune & Stratton, Inc., 1956, Vol. 1, pp. 91-137.

8. Itano, H. A.; Bergren, W. R., and Sturgeon, P.: The Abnormal Human Hemoglobins, Medicine 35:121-159, 1956.

9. Neel, J. V.: The Genetics of Human Hemoglobin Differences, Problems and Perspectives, Ann. Human Genet. 21:1-30, 1956.

10. Neel, J. V.: Human Hemoglobin Types: Their Epidemiological Implications, The Cutter Lecture for 1956, New England J. Med., to be published.

Blood Disorders Caused by Drug Sensitivity

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The Problem

In 1922, Werner Schultz [1] described a syndrome which ultimately came to be known as agranulocytosis. At first but a few cases were recognized, but between 1929 and 1934 a large number were reported. About this time (1931) Kracke [2] noted that the sudden appearance and growing number of cases of agranulocytosis corresponded with the introduction of certain coal-tar derivatives as therapeutic agents. The disorder was especially common in the countries in which such drugs were in great use, and those affected were chiefly women of good economic status as well as nurses and other medical workers to whom these drugs were easily accessible. Shortly afterward several reports appeared * which incriminated aminopyrine (Pyramidon) as the offending drug. After 1934 the number of cases of agranulocytosis began to decrease. This coincided with the reduced sales of aminopyrine following reports of its injurious effects.[5]

Later, however, as new drugs were introduced, new cases appeared. A pattern was repeated which has now become a familiar one. A new agent is described and in a few years it is widely used. At first it is hailed as being nontoxic; ultimately a report appears describing the development of agranulocytosis in association with its use. This is followed by another case, and another, and the circumstantial evidence becomes impressive. The drug loses popularity, and it is employed with more discrimination than before. The number of cases of agranulocytosis associated with the use of this agent decreases sharply, only to be replaced by others as new drugs are added to the therapeutic armamentarium.

With the ever-increasing number of therapeutic agents, as well as with the greatly increased use of chemicals of one kind or another in the toilette, for use as household aids or in hobbies, and in industry, the problem of the toxic effects of various agents on the hemopoietic system has become a serious one. Furthermore, it has become clear that not only may granulocytopenia and a syndrome of agranulocytosis develop in association with exposure to certain chemical agents, but thrombocytopenia and purpura as well as pancytopenia with depression of all three formed elements of the blood may also develop. In addition to these disturbances of the hemopoietic system, occasionally instances of hemolytic anemia are encountered.

It has long been known that certain chemical agents (benzene, potassium arsenite solution), as well as ionizing radiation, are capable of producing profound disturbances in the hemopoietic system.[6] In recent years additional drugs of this character have been discovered, such as mechlorethamine hydrochloride (nitrogen mustard), urethan, and other compounds (Table 1). Such agents have a more or less predictable effect on the hemopoietic system; the deleterious effects are more or less proportional to the amount given within a limited period of time. Because of these effects, these agents have become very useful in the palliative manage-

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* References 3-5.

TABLE 1.—*Agents Associated with the Predictable Development of Hematopoietic Disorders*

Physical:	Roentgen rays
	Radioactive agents (phosphorus, gold, etc.)
Chemical:	Mechlorethamine hydrochloride
	Triethylene melamine
	Urethan
	Benzene
	Bisulfan (Myleran)
	Demecolcine
	Antimetabolites
	Phenylhydrazine

ment of a number of hemopoietic disorders, such as the leukemias and Hodgkin's disease.

The problem under discussion today, however, is not one posed by the use of these agents. We are concerned with the unpredictable, deleterious reactions which occur in occasional persons. The syndrome first recognized in association with the taking of aminopyrine develops only in a very small proportion of those taking the offending drug. Thus, in a series of 400 cases of arthritis in which aminopyrine was used as a therapeutic agent, agranulocytosis developed in only four.[7] In another series, of 103 cases, agranulocytosis was not encountered at all.[8] In association with the administration of thiouracil, a reduction in the leucocyte count to less than 3000 per cubic millimeter with slight to marked granulocytopenia was observed in 3.4% of 781 patients taking this agent, and a depression or absence of granulocytes together with infection in the throat and neck developed in 1.7% of 1091 cases.[9] Leucopenia was observed in only 1.5% of 672 patients treated with propylthiouracil[10] and was stated to have occurred in 4.1% of 1886 patients given methylthiouracil.[11] Neutropenia was noted in only three of 460 patients given sulfadiazine,[12] and acute agranulocytosis has been stated as occurring in 1% of patients treated with amithiozone (Tibione).[13] Again, aplastic anemia was estimated to occur only once among 25,000 persons given quinacrine as an antimalarial agent.[14] The problem, then, is one of unpredictable toxicity. Standard methods for evaluation of the toxicity of a therapeutic agent carried out in pharmacological laboratories on suitable test animals have failed to reveal the type of individual sensitivity or idiosyncrasy under discussion here.

The Agents

In Table 2 are listed some of the agents which have been reported to have been associated occasionally with the occurrence of leucopenia and granulocytopenia. A more complete list has been published elsewhere.[6] In Table 3 some of the agents reported to have been associated with the development of thrombocytopenia and purpura are listed. It will be noted that these are fewer in number than those associated with the occurrence of granulocytopenia. In Table 4 are presented a number of the agents which have been observed to be associated with the

TABLE 2.—*Incidence of Leucopenia and Agranulocytosis*

Drug	No. Receiving Drug	No. with Blood Changes	Per Cent
Aminopyrine[7]	400	4	1.0
Aminopyrine[8]	103	0	0
Thiouracil[9]	1091	19	1.7
Propylthiouracil[10]	672	10	1.5
Methylthiouracil[11]	1886	77	4.1
Sulfadiazine[12]	460	3	0.6

TABLE 3.—*Agents Occasionally Associated with the Occurrence of Leucopenia (Granulocytopenia)*

Analgesics	Aminopyrine (and others), Phenylbutazone
Antithyroid drugs	Thiouracil (and others), carbimazole, etc.[6]
Anticonvulsants	Trimethadione, etc.[6]
Sulfonamides	Sulfathiazole, sulfisoxazole (Gantrisin), etc.[6]
Antihistaminics	Tripelennamine (Pyribenzamine), etc.[6]
Antimicrobial agents	Chloramphenicol, organic arsenicals, etc.[6]
Miscellaneous	Chlorpromazine, Dinitrophenol, etc.[6]

TABLE 4.—*Agents Occasionally Associated with the Occurrence of Thrombocytopenic Purpura*

Sulfonamides
Sedormid (allylisopropylacetylcarbamide)
Quinidine, quinine
Gold salts
Organic arsenicals
And possibly..Oxytetracycline
Aminosalicylic acid
Phenylbutazone
Trimethadione, etc.[4]

developent of pancytopenia, or aplastic anemia. In Table 5 some of the agents associated with the development of hemolytic anemia are listed. A more complete tabulation is given elsewhere.[6]

TABLE 5.—*Agents Occasionally Associated with the Occurrence of Pancytopenia*

	20–30 or More Cases	Single or Very Few Reports
Antimicrobial agents	Arsenobenzols	Streptomycin
	Chloramphenicol	Sulfonamides
		Tetracyclines
Anticonvulsants	Mesantoin (3-methyl-5,5-phenylethylhydantoin)	Trimethadione (Tridione)
		Nuvarone (3-methyl-5-phenylhydantoin)
Antithyroid drugs		Methimazole (Tapazole)
Antihistaminics		Tripelennamine (Pyribenzamine)
Insecticides		DDT (dichlorodiphenyl-trichloroethane)
Miscellaneous agents	Gold compounds	Quinacrine
	Trinitrotoluene	Dinitrophenol
		Phenylbutazone
		Chlorpromazine, etc.[4]

The Patient's History

The history in the reported cases has often been pretty much the same. A therapeutic agent was given to a patient in customary doses. No deleterious effect was expected or observed. After the drug had been administered again for one or more times, sore throat, purpura, weakness, pallor, or other related manifestations appeared, which led to examination of the blood, and granulocytopenia, thrombocytopenia, both these changes together with anemia (pancytopenia), or hemolytic anemia were discovered.

TABLE 6.—*Chemical Agents Occasionally Associated with the Occurrence of Hemolytic Anemia*

Sulfonamides
Quinine
Pamaquine, primaquine
Aminosalicylic acid
Phenothiazine
Amphetamine (Benzedrine)
Mesantoin (3-methyl-5,5-phenylethylhydantoin)
Stibophen (Fuadin), etc.[4]

This is not the invariable pattern, however, and at times the hemopoietic catastrophe has been observed to develop in association with the first known exposure to the agent in question. The time interval between the administration of the drug and the development of the deleterious changes has varied from a few days to a few weeks.

It should be emphasized that in the case of most of the agents under consideration here, the quantity of drug employed appears to have been of no importance. Thus, fatal agranulocytosis has been observed to occur following the taking of even a single dose of aminopyrine. A number of investigators have shown that, following recovery from an attack of agranulocytosis, administration of small amounts of the suspected agent was followed within 6 to 10 hours by disappearance of all the neutrophiles from the blood.† It is noteworthy that preceding the granulocytopenia a sensation of general malaise as well as a chill and fever sometimes developed.

Pathogenesis

In the situations under discussion here,

† References 3, 4, 15, and 16.

the assumption that the therapeutic agent in question was the cause of the untoward changes in the hemopoietic system is founded on circumstantial evidence. As a matter of fact, with certain drugs the incidence of deleterious effects has been so low [6] that one wonders whether in these cases the occurrence of the hemopoietic changes was not purely coincidental. Thus, the reports incriminating the barbiturates as a cause of granulocytopenia are very few [17] in comparison to their wide use. On the other hand, the circumstantial evidence in other instances is such that one finds it difficult to avoid the conclusion that the drug and the blood changes were related to one another.

Unfortunately, however, attempts to prove the toxicity of such agents have not met with success, nor has a means been devised whereby these occasional instances of toxicity can be predicted. The pathogenesis of this form of hemopoietic damage is quite obscure.

Kracke [2] pointed out that the drugs producing agranulocytosis were those of the "benzamine" group (benzene ring with an attached amine) and suggested that their action might be a leucotoxic effect due to an oxidation product. This suggestion is pertinent even today, for chloramphenicol is a substituted nitrobenzene. No evidence has been produced, however, which would indicate that the action of drugs such as aminopyrine represents a simple toxic effect; the feeding or injection of aminopyrine to rabbits, guinea pigs, dogs, rats, and monkeys ‡ has failed to produce any deleterious effects on the hemopoietic system. Neither have we been able to demonstrate a simple toxic effect of chloramphenicol in normal or in nutritionally deficient rats. It has been noted, however, that some of the drugs which may produce agranulocytosis occasionally in man may be the cause of symptoms and signs which are usually considered to be manifestations of idiosyncrasy, such as rash, urticaria, edema, and asthma. This observation, together with the fact that the amount of the drug consumed has often been very small and also because the harmful effects have often appeared after the second or a still later exposure to the drug rather than after the first dose, suggest that the untoward reaction to these drugs is that of a process involving sensitization. Several interesting studies have been carried out.

Ackroyd,§ in 1949, observed that the administration of Sedormid to persons whose history indicated that they developed purpura on taking this drug was followed by pronounced thrombocytopenia within 30 to 60 minutes. This led to in vitro experiments in which it was shown that agglutination followed by lysis of platelets occurred when Sedormid was added to the blood of patients who had recovered from attacks of purpura caused by it. The concentrations used corresponded to those to be expected with therapeutic administration of the drug. It was shown that the platelet lysis was the result of the reaction of some factor in the plasma acting in the presence of Sedormid and was not due to any peculiarity of the platelets themselves. Normal serum had no such effect and the omission of Sedormid (allylisopropylacetylcarbamide) gave negative results. Inactivated serum produced only agglutination of platelets upon incubation with Sedormid, but the addition of complement resulted in platelet lysis. These observations led to the suggestion that the combination of Sedormid and platelets serves as the antigen and that the presence of both is required for agglutination and lysis by the antibody present in the plasma.

A similar mechanism has been demonstrated in thrombocytopenic purpura which developed following the taking of quinidine.[25] Antibodies were demonstrated in the patients' blood for as long as six months following discontinuance of quinidine therapy, even though the thrombocytopenia had subsided completely. It is of interest that the reaction is so specific that negative results have been observed in quinidine- sensi-

‡ References 18-21.

§ References 22-24.

tive cases when its levorotatory isomer, quinine, was used. Quinine, however, may produce thrombocytopenia in its own right. In quinine-sensitive persons, in vitro agglutination and lysis of platelets following the addition of quinine have been demonstrated.[26] Furthermore, the critical role of the chemical in the pathogenesis of the thrombocytopenia has been demonstrated by the induction of thrombocytopenia in a normal subject who was given quinine by mouth following transfusion of the plasma of a patient sensitive to this agent.[27]

Newer studies have brought fresh concepts concerning the mechanism whereby agranulocytosis develops in sensitive persons. The observation that in this condition there is a scarcity of juvenile and segmented neutrophilic leucocytes in the bone marrow, less mature forms being plentiful, led originally to the suggestion that the primary disturbance is a failure of maturation of granulocytes ("maturation arrest"). This concept failed to take into consideration other possibilities. In particular, it ignored the observation that the leucopenia may be observed to develop in an interval as short as six hours following the ingestion of the offending drug.[5] To account for so rapid a disappearance of the cells, abnormal peripheral destruction of the polymorphonuclear leucocytes or segregation of the cells such as would occur if they should stick to the capillary endothelium would have to be postulated rather than arrested maturation.

Attempts to demonstrate an antigen-antibody type of reaction in cases of agranulocytosis have led to the observation that the transfusion of blood withdrawn three hours after the administration of a test dose of aminopyrine to a sensitive patient produced outspoken granulocytopenia in two normal subjects.‖ This granulocytopenia lasted three to five hours. In the plasma and serum of the sensitive person a substance was found which produced agglutination of homologous and heterologous leucocytes in vitro. The leucocyte agglutinating substance was found to be a globulin. Subsequent studies indicated that destruction of the agglutinated leucocytes occurred in vivo, probably in the lung capillaries. Thus the changes in the bone marrow previously attributed to maturation arrest can more readily be attributed to a precipitate depletion and exhaustion of the bone marrow as the result of the greatly increased peripheral destruction of the granulocytes. Moeschlin and his associates¶ postulated that an offending drug combines with a protein in the serum to form an antigen. This causes sensitization, and the antibodies so formed become attached to the leucocytes, which are then agglutinated and destroyed when the leucocyte-bound antibody and antigen come in contact. These observations have been confirmed by other investigators.#

That a somewhat similar mechanism may be involved in the development of some cases of hemolytic anemia, perhaps by interaction of the chemical agent with the red cells and the production of antibodies against the chemically changed cells, is suggested by observations in a patient in whom an acute hemolytic episode developed during the readministration of stibophen (Fuadin).[38] In the presence of this drug or of a chemically related compound the serum of the patient agglutinated the patient's or normal red cells, and it sensitized normal red cells so that they became positive upon Coombs' testing. The stibophen-requiring agglutinin could be transferred passively and could be activated in vivo, by the administration of this drug to the normal recipient.

Of even more interest, because it reveals a mechanism explaining individual sensitivity not hitherto given serious consideration, is the observation made by Dern and his associates.* Investigating the observation that Negroes are more likely to develop acute hemolytic anemia from pamaquine

‖ References 28-32.

¶ References 28-32.

References 33-37.

* References 39-43.

than white patients [44] and that about 10% of American Negroes are susceptible to hemolysis by primaquine, these investigators were able to show that this susceptibility resides in the subject's erythrocytes. The erythrocytes of a susceptible subject, tagged with radiochromium and transferred into a nonsentitive subject, were hemolyzed when primaquine was given to the recipient. It was further demonstrated that the administration of primaquine to drug-sensitive recipients with resulting acute hemolysis was followed by complete recovery although drug administration was continued. The self-limitation of the hemolysis was shown to be due to a change in the reactivity of the red cell population. The sensitive cells were found to be the older ones; the sensitivity has been shown to be related to a wearing out of the mechanisms for maintaining an adequate level of glutathione in red cells.[48]

Much more obscure is the pathogenesis of the aplastic anemias associated with the taking of certain drugs. The observation that chloramphenicol was associated with the occurrence of aplastic anemia [6] led to a number of studies, but none of these has revealed the mechanism underlying this effect. Anemia has been reported in ducks fed chloramphenicol,[46] but prolonged administration has had no ill effects in mammals.[47] It has been noted that the in vitro respiration of leucocytes is impaired by chloramphenicol,[48] but it is difficult to see how this is related to the occasional development of aplastic anemia. In our own laboratory, in experiments conducted by Dr. A. J. Samuels,† a variety of attempts were made to sensitize rabbits to chloramphenicol and various derivatives of this drug by conjugating these with rabbit-bone-marrow protein and injecting the protein-bound drug intramuscularly together with a Freund type adjuvant. Attempts were also made to sensitize guinea pigs to aminopyrine and to chloramphenicol by repeatedly injecting erythrocytes previously incubated in vitro with one of these drugs. By none of these procedures was it possible to produce hemopoietic disturbances.

Solution of the Problem

The problems posed by sensitivity to drugs and various other chemical agents are not easily solved. There are, however, certain obvious steps which can be taken.

A very disturbing feature of the histories of many cases in which drug sensitivity was associated with very serious and sometimes even fatal effects is the fact that the drugs in question were often employed when there was no very good indication for their use. Thus, for example, our first instance of aplastic anemia associated with the taking of chloramphenicol occurred in a young man who had been given this agent for the treatment of peptic ulcer.[49] On the return of the symptoms of the ulcer, the chloramphenicol was taken again, and fatal aplastic anemia developed. In another instance of fatal aplastic anemia chloramphenicol had been prescribed for an upper respiratory tract infection. Subsequently, the patient's mother, not having been warned that chloramphenicol might be dangerous, followed the example of the physician and administered this drug of her own accord on subsequent occasions when her child developed "the sniffles."

It is obviously important that physicians avoid the indiscriminate use of therapeutic agents and that they understand the potential danger of many of the drugs we use today. The rare untoward effects of various agents should not prevent their use whenever they are specifically indicated and where no less potentially toxic agent is available. The public must also be aware of the dangers and must avoid self-medication. It is most difficult to impress some physicians with these principles. It is also easier to give the lay public the false impression that a new therapeutic agent is a "magic bullet" than to arouse an attitude of caution and a

† These studies were supported by a grant from the American Drug Manufacturers' Association.

sense of potential danger as well as the promise of great value.

Since no adequate means has been discovered so far for the detection of the potential toxicity of an agent in occasional patients, a system must be devised whereby physicians may be alerted promptly when danger signals appear. Hitherto there has always been a lag of several years between the occurrence of untoward effects in occasional persons in different parts of the world and the dissemination of such information and recognition of the possible cause of the hemopoietic disorders. A subcommittee of the A. M. A. Council on Pharmacy and Chemistry's Committee on Research is now attempting to devise a reporting and warning system which may help to avoid some of the unhappy results which have been observed hitherto.

Summary

A number of the agents occasionally associated with the development of blood dyscrasias are listed. There appear to be several mechanisms whereby such dyscrasias may develop. As yet no means has been devised whereby the potential toxicity of an agent or the sensitivity of an occasional subject may be detected. It is therefore all the more necessary that therapeutic agents be used with discrimination and that the public avoid self-medication. A method for prompt reporting of observed untoward effects and rapid warning of physicians is being worked out.

REFERENCES

1. Schultz, W.: Über eigenartige Halserkrankungen, Deutsche med. Wchnschr. 48:1495, 1922.

2. Kracke, R. R.: Recurrent Agranulocytosis, Am. J. Clin. Path. 1:385, 1931.

3. Madison, F. W., and Squier, T. L.: The Etiology of Primary Granulocytopenia (Agranulocytic Angina), J. A. M. A. 102:755, 1934.

4. Squier, T. L., and Madison, F. W.: Primary Granulocytopenia Due to Hypersensitivity to Amidopyrine, J. Allergy 6:9, 1934.

5. Plum, P.: Clinical and Experimental Investigations in Agranulocytosis, London, H. K. Lewis & Co., Ltd., 1937, p. 410.

6. Wintrobe, M. M.: Clinical Hematology, Ed. 4, Philadelphia, Lea & Febiger, 1956.

7. Rawls, W. B.: The Effect of Amidopyrine upon the Red, White and Polymorphonuclear Blood Cells of a Series of 100 Patients, Am. J. M. Sc. 192:175, 1936.

8. Simon, S. D., and Metz, M. H.: Amidopyrine and the Circulating Leucocytes, J. Lab. & Clin. Med. 21:1154, 1936.

9. Moore, F. D.: Toxic Manifestations of Thiouracil Therapy, J. A. M. A. 130:315, 1946.

10. Bartels, E. C.: Agranulocytosis During Propylthiouracil Therapy, Am. J. Med. 5:48, 1948.

11. Pulver, W., and Spillmann, W.: Agranulocytose und Methylthiouracil, Schweiz. med. Wchnschr. 83:538, 1953.

12. Finland, M.; Peterson, O. L., and Goodwin, R. A., Jr.: Sulfadiazine: Further Studies of Its Efficacy and Toxic Effects in 460 Patients, Ann. Int. Med. 17:920, 1942.

13. Davis, J. A., Jr.; Viehman, A. J., and Frommeyer, W. B., Jr.: Acute Agranulocytosis During the Use of Tibione: Report of Case, South. M. J. 45:861, 1952.

14. Custer, R. P.: Aplastic Anemia in Soldiers Treated with Atabrine (Quinacrine), Am. J. M. Sc. 212:211, 1946.

15. Astwood, E. B.: Thiouracil Treatment in Hyperthyroidism, J. Clin. Endocrinol. 4:229, 1944.

16. Rohr, K.: Der heutige Stand der Agranulozytoseforschung, Helvet. med. acta 6:611, 1939.

17. Hadler, A. J.: Granulocytopenia Following Barbiturate Therapy, New England J. Med. 222: 755, 1940.

18. Climenko, D. R.: The Modification of the Hematopoietic Function in the Rabbit by Certain Cyclic Compounds, J. Lab. & Clin. Med. 21:913, 1936.

19. Hansen, A. B.: Some Investigations on Experimental Agranulocytosis in Rabbits, Acta med. scandinav. 98:307, 1939.

20. Holten, C.: Considerations and Experiments on the Hypersensitive Nature of Amidopyrine Agranulocytosis, Am. J. M. Sc. 194:229, 1937.

21. Wilson, S. J.: Effects of Aminopyrine and Phenobarbital on Blood Cell Count of White Rats, Kansas M. Soc. J. 36:500, 1935.

22. Ackroyd, J. F.: The Pathogenesis of Thrombocytopenic Purpura Due to Hypersensitivity to Sedormid (Allyl-Isopropyl-Acetyl-Carbamide), Clin. Sc. 7:249, 1949.

23. Ackroyd, J. F.: The Mechanism of the Reduction of Clot Retraction by Sedormid in the Blood of Patients Who Have Recovered from Sedormid Purpura, Clin. Sc. 8:235, 1949.

24. Ackroyd, J. F.: The Cause of Thrombocytopenia in Sedormid Purpura, Clin. Sc. 8:269, 1949.

25. Weisfuse, L.; Spear, P. W., and Sass, M.: Quinidine-Induced Thrombocytopenic Purpura, Am. J. Med. 17:414, 1954.

26. Bolton, F. G., and Young, R. V.: Observations on Cases of Thrombocytopenic Purpura Due to Quinine, Sulphamezathine, and Quinidine, J. Clin. Path. 6:320, 1953.

27. Steinkamp, R.; Moore, C. V., and Doubek, W. G.: Thrombocytopenic Purpura Caused by Hypersensitivity to Quinine, J. Lab. & Clin. Med. 45:18, 1955.

28. Moeschlin, S., and Wagner, K.: Agranulocytosis Due to the Occurrence of Leukocyte-Agglutinins (Pyramidon and Cold Agglutinins), Acta haemat. 8:29, 1952.

29. Moeschlin, S.; Meyer, H.; Israels, L. G., and Tarr-Gloor, E.: Experimental Agranulocytosis: Its Production Through Leukocyte Agglutination by Antileukocytic Serum, Acta haemat. 11:73, 1954.

30. Moeschlin, S., and Moreno, R.: Pyramidon-Agranulocytose mit Agglutininen für Arteigene und artfremde Leukocyten, Klin. Wchnschr. 32:799, 1954.

31. Schmidt, W., and Moeschlin, S.: Physikalischchemische und serologische Untersuchungen von Antileukocytenserum, Ärztl. Forsch. 8:229, 1954.

32. Moeschlin, S.: Immunological Granulocytopenia and Agranulocytosis: Clinical Aspects, Sang 26:32, 1955.

33. Dausset, J., and Nenna, A.: Présence d'une leuco-agglutinine dans le sérum d'un cas d'agranulocytose chronique, Compt. rend. Soc. biol. 146: 1539, 1952.

34. Dausset, J.; Nenna, A.; Tsevrenis, H., and Bernard, J.: Leuco-agglutinines (IV): La Pancytopénie chronique idiopathique avec leuco-agglutinine sérique, Rev. hémat. 8:316, 1953.

35. Dausset, J., and Nenna, A.: Présence d'une leuko-agglutinine dans trois sérums de maladies leucópéniques, Sang 24:410, 1953.

36. Dausset, J.: Leuco-Agglutinins IV: Leuco-Agglutinins and Blood Transfusion, Vox sanguinis 4:190, 1954.

37. Goudsmit, R., and van Loghem, J. J., Jr.: Studies on the Occurrence of Leucocyte-Antibodies, Vox sanguinis 3e:58, 1953.

38. Harris, J. W.: Studies on the Mechanism of a Drug-Induced Hemolytic Anemia, J. Lab. & Clin. Med. 47:760, 1956.

39. Dern, R. J.; Weinstein, I. M.; LeRoy, G. V.; Talmage, D. W., and Alving, A. S.: The Hemolytic Effect of Primaquine: I. The Localization of the Drug-Induced Hemolytic Defect in Primaquine-Sensitive Individuals, J. Lab. & Clin. Med. 43:303, 1954.

40. Dern, R. J.; Beutler, E., and Alving, A. S.: The Hemolytic Effect of Primaquine: II. The Natural Course of the Hemolytic Anemia and the Mechanism of Its Self-limited Character, J. Lab. & Clin. Med. 44:171, 1954.

41. Beutler, E.; Dern, R. J., and Alving, A. S.: The Hemolytic Effect of Primaquine: IV. The Relationship of Cell Age to Hemolysis, J. Lab. & Clin. Med. 44:439, 1954.

42. Dern, R. J.; Beutler, E., and Alving, A. S.: The Hemolytic Effect of Primaquine: V. Primaquine Sensitivity as a Manifestation of a Multiple Drug Sensitivity, J. Lab. & Clin. Med. 45:30, 1955.

43. Beutler, E.; Dern, R. J., and Alving, A. S.: The Hemolytic Effect of Primaquine: VI. An in Vitro Test for Sensitivity of Erythrocytes to Primaquine, J. Lab. & Clin. Med. 45:40, 1955.

44. Earle, D. P., Jr.; Bigelow, F. S.; Zubrod, C. G., and Kane, C. A.: Studies on Chemotherapy of Human Malarias: Effect of Pamaquine on the Blood Cells of Man, J. Clin. Invest. 27:121, (May Pt. 2) 1948.

45. Beutler, E.: In Vitro Studies of the Stability of Red Cell Glutathione: A New Test for Drug Sensitivity, J. Clin. Invest. 35:690, 1956.

46. Rigdon, R. H.; Crass, G., and Martin, N.: Anemia Produced by Chloramphenicol (Chloromycetin) in the Duck, A. M. A. Arch. Path. 58:85, 1954.

47. Saslaw, S.; Stevenson, T. D., and Doan, C. A.: Prolonged Administration of Chloramphenicol in Monkeys, Proc. Soc. Exper. Biol. & Med. 85:295, 1954.

48. Follette, J. H.; Shugarman, P. M.; Reynolds, J.; Valentine, W. N., and Lawrence, J. S.: The Effect of Chloramphenicol and Other Antibiotics on Leukocyte Respiration, Blood 11:234, 1956.

49. Smiley, R. K.; Cartwright, G. E., and Wintrobe, M. M.: Fatal Aplastic Anemia Following Chloramphenicol (Chloromycetin) Administration, J. A. M. A. 149:914, 1952.

Newer Agents in the Treatment of Leukemia

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It is intended in this paper to summarize the status of the newer agents which are available for the treatment of leukemia. Exhaustive coverage of this subject is obviously impossible in a brief review.

In discussing therapy it is best to consider acute leukemia and the chronic leukemias as two separate groups, since there are certain major differences in approach.

The agents available for the treatment of acute leukemia may be divided into two large classes. First, the steroid hormones, of which cortisone, hydrocortisone, corticotropin (ACTH) and prednisone are examples. In this group, it appears that prednisone and prednisolone have certain advantages over cortisone, since they produce less of the undesirable side-effects on electrolyte balance for the same degree of therapeutic effect. The original observations of the value of corticotropin in leukemia were made by Pearson and co-workers [1] and Farber and co-workers.* The steroids act rapidly and are therefore of greatest value in the treatment of the severely ill patient with a hemorrhagic diathesis where rapidity of action is essential. They are particularly effective in children, less so in young adults, and least effective in adults over 30 years of age. The use of steroids in massive doses has been pioneered by Bernard [4] in Paris and Hill [5] in this country. These workers feel that with cortisone or prednisone in doses ranging from 1 to 5 gm. daily, remissions can be achieved in adults who would not ordinarily be expected to respond to more conventional doses of steroids. Even with prednisone, sodium retention, hypertension, and impaired carbohydrate metabolism occur at these dose levels, but this form of therapy appears to be definitely promising and requires further study.

The second group of useful agents may be classified as antimetabolites. This group may be subdivided into the folic acid antagonists, the purine antagonists, and the glutamine antagonists. The folic acid antagonists, of which we feel that amethopterin (Methotrexate) is the preferred compound, were first shown to be active against leukemia by Farber and co-workers.[6] They are very useful in the treatment of the disease in children but are much less effective in young adults and are rarely, except in special situations, useful in adults. Amethopterin has a better therapeutic index in mouse tumors and leukemias than aminopterin,† and, since we have been using it exclusively, we have noted less toxicity and better therapeutic results in the acute leukemias.[10] The usual dose for a 5-year-old child is 2.5 mg. daily by mouth. Maintenance or intermittent therapy may be given, but it appears easier to manage the

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* References 2 and 3.

† References 7-9.

patients on maintenance therapy, and there is no interference with growth. The folic acid antagonists, as all the antimetabolites, act more slowly than the steroids and require three to eight weeks to exert their beneficial effect. The remissions they produce, however, are usually considerably longer than with the steroids and somewhat longer than with mercaptopurine.

In a second subdivision among the antimetabolites with antileukemic effect are the purine antagonists.[11] The active members of this group are mercaptopurine (Purinethol), given in a dose of 2.5 mg/kilogram daily by mouth; Thioguanine (6-mercapto-2-amino-purine), given in the same dosage; and 6-chloropurine, at a dose of 15-20 mg/kilogram daily. With these agents also, three to eight weeks of treatment is necessary before a beneficial effect is apparent. The remissions produced with them are slightly shorter than those with amethopterin but longer than with the steroids. At the present time in the treatment of acute leukemia in children it does not appear that either chloropurine or Thioguanine has any advantage over mercaptopurine.[12] In adults, preliminary studies by Ellison[13] in a small series of cases have suggested that chloropurine in a dose of 1 gm. daily P.O. causes a slightly higher incidence of remissions in older adults than mercaptopurine, but this may well have been a result of the relative dosage given, since studies elsewhere with higher doses of mercaptopurine have given a higher incidence of remissions.[14]

A third group of the antimetabolites which is worthy of mention consists of the so-called glutamine antagonists, such as azaserine and DON (6-diazo-5-oxo-L-norleucine). These two compounds, derived from antibiotic preparations, demonstrate considerable effects against animal tumors and leukemias ‡ but have no practical value alone in human leukemia. Experimental studies in mice with Sarcoma 180[18] and in leukemic mice § have shown definite synergistic effects with 6-mercaptopurine, however, and preliminary studies have suggested, particularly in children, that when used in combination with mercaptopurine they may delay for a short time the development of resistance to mercaptopurine.[10]

Biochemical studies by Buchanan,|| by Skipper,¶ and by Elion[25] have pinpointed the sites of action of these compounds and have suggested the rationale for this combination therapy. DON and Azaserine (O-diazoacetyl-L-serine) apparently act to prevent the conversion of formyl glycide amide ribotide to formyl glycine amidine ribotide, a step in the *de novo* synthesis of nucleic acid purines, whereas mercaptopurine presumably acts to prevent the conversion of a preformed purine, such as inosinic acid, to the adenine and guanine of the nucleic acids.

Figure 1 shows data on a child with acute leukemia under treatment for 18 months with the combination of mercaptopurine and Azaserine, who finally developed resistance but who now is in a second remission on amethopterin therapy. It is too early to say for certain that the combination of mercaptopurine and Azaserine is better than 6-mercaptopurine alone, and carefully controlled randomized studies at 12 cooperating centers are in progress at the present time under the auspices of the Clinical Studies Panel of the Cancer Chemotherapy National Service Center to determine the significance of these observations.

With these three general classes of agents available for use, the question of which to use originally must be decided. Our decisions are based on two facts: 1. That the steroids work rapidly, particularly in patients with a hemorrhagic diathesis, but that the remissions are of fairly short duration, and 2. that the antimetabolites, on the other hand, take longer to exert their beneficial effects, but that the remissions also last longer. Therefore, we feel that the antimetabolites should be the main reliance of

‡ References 15-21.

§ References 20 and 21.

|| Reference 22. Buchanan, J. M.: Personal communication to the authors.

¶ References 23 and 24.

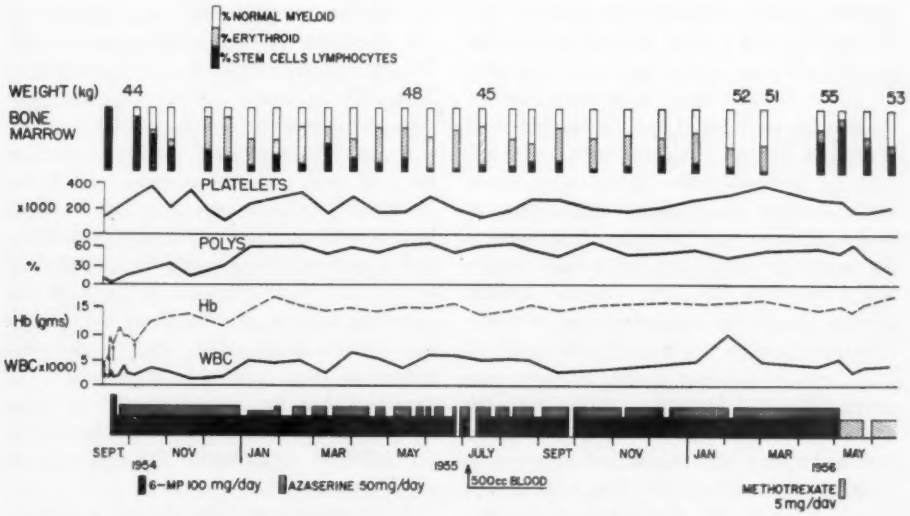

Fig. 1.—Remission with mercaptopurine and Azaserine with development of resistance and a second remission with amethopterin (Methotrexate).

the chemotherapist and the backbone of long-range therapy. The steroids are extremely valuable agents and act so rapidly at a time when no other agent will work that they therefore should be saved for just such emergencies and should not be used in antimetabolite-suitable cases. Therefore, we feel that the patients should be divided into two categories: 1. Those who are suitable for antimetabolite therapy and 2. those who require steroids. Thus, in an acutely ill patient with a hemorrhagic diathesis, be it a child, young adult, or older adult, steroids are suggested for initial therapy. For a child less acutely ill, we would use amethopterin, mercaptopurine, or the combination of mercaptopurine and Azaserine. For the young adult and for the older adult, mercaptopurine is the antimetabolite which should be used initially.

Fortunately, there is no cross resistance between these three types of agents, and a patient developing resistance to one may still be expected to respond to the others. Of considerable interest in this regard is the observation by Law and co-workers [26] on mouse leukemia that strains developing resistance to mercaptopurine have then an increased sensitivity to amethopterin. Preliminary studies by Ellison [13] on adults with acute leukemia who have become resistant to mercaptopurine appears to indicate that in some of these amethopterin will produce a complete remission. Remissions from amethopterin would not ordinarily be expected in this age group.

Figure 2 shows the effects of these various drugs on the survival time of children with acute leukemia. There are four different groups of children with acute leukemia: (1) A group of 218 children with acute leukemia without specific treatment,

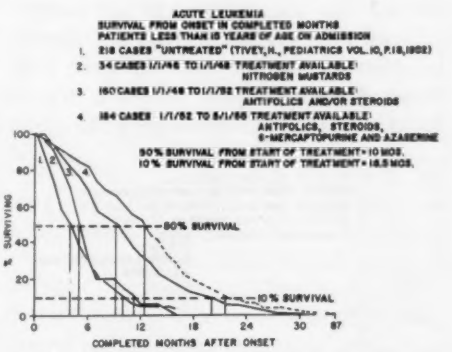
ACUTE LEUKEMIA
SURVIVAL FROM ONSET IN COMPLETED MONTHS
PATIENTS LESS THAN 18 YEARS OF AGE ON ADMISSION
1. 218 CASES "UNTREATED" (TIVEY, H., PEDIATRICS VOL. 10, P. 18, 1952)
2. 34 CASES 1/1/46 TO 1/1/48 TREATMENT AVAILABLE: NITROGEN MUSTARDS
3. 160 CASES 1/1/48 TO 1/1/52 TREATMENT AVAILABLE: ANTIFOLICS AND/OR STEROIDS
4. 184 CASES 1/1/52 TO 8/1/56 TREATMENT AVAILABLE: ANTIFOLICS, STEROIDS, 6-MERCAPTOPURINE AND AZASERINE
50% SURVIVAL FROM START OF TREATMENT = 10 MOS.
10% SURVIVAL FROM START OF TREATMENT = 18.5 MOS.
% SURVIVING
50% SURVIVAL
10% SURVIVAL
COMPLETED MONTHS AFTER ONSET

Fig. 2.—The effects of antimetabolites on the survival time of children with acute leukemia.

collected from the literature by Tivey.[27] The median survival time is approximately four months. (2) A similar group, of 34 children, who did not have the benefit of any of the modern methods of specific therapy were treated at Memorial Center with mechlorethamine hydrochloride. They were given just as many transfusions and almost as many antibiotics as the other groups with the same therapeutic zeal but did not receive any compounds we now consider specific agents. Again the survival time was approximately four to five months. (3) A group of 154 children treated between January, 1948, and December, 1951, with the folic acid antagonists or the steroids or both had a median survival time of approximately nine months. (4) The final group, in which treatment was initiated between Jan. 1, 1952, and May 1, 1955, had the advantage that mercaptopurine and Azaserine were available for their treatment in addition to the other agents. These are 184 consecutive cases, and it is obvious that some were acutely ill and died after only a few doses of steroids. These cases are naturally included, since the other drugs were available for their treatment if it had seemed indicated. In this group the median survival time was increased to 12.4 months.

When these median survival time figures in children, however, are contrasted with those achieved in adults, as seen in Figure 3, the results are less encouraging. In adults the median survival time is still approximately seven months. These figures are influenced markedly by the fact that in only 20%-25% of adults can a complete remission be achieved by any form of treatment. Haut and co-workers[28] report a median survival time of eight months in a series in which remission was achieved in 33%. However, their series included both children and adults, which accounts for the slightly better rate of remissions. Actually, if one takes the median survival time of the adult patients in our group in whom a complete remission was achieved, it averages 11 months,[13] but the increased survival time in this small segment of the population is not sufficient to influence the over-all survival time statistics markedly.

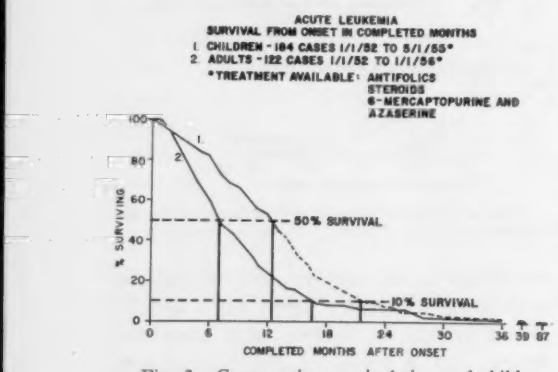

Fig. 3.—Comparative survival times of children and adults with acute leukemia.

In the treatment of the chronic leukemias, as can be seen in the Table, there are five general groups of chemotherapeutic agents which can be used. In chronological order, they are arsenic, urethan, the polyfunctional alkylating agents, the colchicine derivatives, and the purine antagonists. Since we are discussing only newer agents in the treatment of leukemia, we will disregard arsenic and urethan and will consider only two of the polyfunctional alkylating agents, both of which were developed by the group at the Chester Beatty Institute in London.#

Chemotherapy of Chronic Leukemias

Compound	Granulocytic	Lymphocytic
Arsenic	+	−
Urethan	+	±
Polyfunctional alkylating agents		
HN_2	+	+
Triethylenemelamine (TEM)	+	+
Triethylene thiophosphoramide (Thio-Tepa)	+	+
Busulfan (Myleran)	++	±
Chlorambucil (CB 1348)	?	+
Desacetylmethylcolchicine (Colcemid)	++	−
Purine antagonists	+	−

References 29-32.

These are busulfan (Myleran [1,4-dimethanesulfonoxybutane]) and CB 1348, or chlorambucil (*p*-[di-2-2chlorethyl] aminophenylbutyric acid). The original pharmacological reports suggested that busulfan had a specific effect on myeloid cells and not on lymphocytes. For that reason its use in chronic granulocytic leukemia has been advocated.* It appears that at the present time it is the best agent for use in this form of disease. It can be given by mouth in therapeutic doses of 4-10 mg. daily and maintenance doses of 2-4 mg. daily to twice weekly and will cause remissions in a high percentage of early cases of this disease. Administration is attended by no immediate side-effects, and absorption appears to be reasonably uniform. Like all of the polyfunctional alkylating agents, in excessive doses it does cause marrow hypoplasia, however. Original studies did not appear to show any beneficial effect in chronic lymphocytic leukemia, but more recent studies have suggested that it may have some useful effect in this disease also.[34]

CB 1348, or chlorambucil, is another of the group of polyfunctional alkylating agents. Pharmacologic studies in rats suggested that this compound had a specific effect on lymphocytes rather than polymorphonuclear leucocytes. This paraphenylbutyric acid derivative of mechlorethamine hydrochloride (HN_2) can also be given by mouth and appears to be well absorbed. As with busulfan, there are no undesirable side-effects. It appears particularly useful in the treatment of chronic lymphocytic leukemia and may be less effective than busulfan in the chronic granulocytic form.†

A colchicine derivative, desacetylmethylcolchicine (Colcemid) which differs from colchicine by the removal of an acetyl group and substitution of a methyl group on the amino nitrogen, was developed by Santavy and Reichstein[37] and is reported to produce considerably less toxicity than colchicine for the same degree of antimitotic effect. This compound was first evaluated clinically by Moeschlin and co-workers[38] and has since been studied by several other groups. It will achieve remissions in a high percentage of early cases of chronic granulocytic leukemia when given by mouth in doses of 3-10 mg. daily. Relapse occurs rapidly when therapy is discontinued, and therefore maintenance therapy is indicated at 3-5 mg. daily.

N-Desacetylthiocolchicine[39] has been tried clinically by Huguenin and co-workers[40] and by us.‡ Although it appears to have a definite effect in reducing the leucocyte count in cases of chronic granulocytic leukemia, the responses have not as yet been regular enough to establish a dosage pattern.

In recent years three of the purine antagonists have also been shown to produce remissions with a high degree of regularity in patients in the early stage of chronic granulocytic leukemia. Daily oral dosage of mercaptopurine or Thioguanine at 2.5 mg/kilogram or chloropurine at 15-20 mg/kilogram are all effective, but neither Thioguanine nor chloropurine seem to have any advantage over 6-mercaptopurine. Generally speaking, relapses occur rapidly when these drugs are discontinued, and maintenance therapy must therefore be given. One patient in our series has been in remission on this drug for over three and one-half years, but most patients have been under treatment for shorter periods.

None of these compounds has been in use long enough for comparison with the more conventional x-ray therapy or radiophosphorus in respect to survival time, nor is it possible to compare one drug with another in this respect. Further studies will be required on all these compounds before any definite evaluation can be made, but it must be said at the present time that all these drugs can produce good remissions and have the advantage that they can be given by mouth and do not require the more expen-

* References 30 and 33.

† References 31, 33, 35, 36.

‡ Krakoff, I. H.; Karnofsky, D. A., and Burchenal, J. H.: Unpublished observations.

sive equipment which is needed for radiation or P^{32} therapy.

Summary

In the treatment of acute leukemia, the antimetabolites should be the main reliance of the chemotherapist, and the steroids should be saved for the emergencies in which rapidity of action is essential or other situations in which they alone will exert a beneficial effect.

Of the folic acid antagonists, amethopterin (Methotrexate) appears to be the most easily handled.

The status of combination therapy with mercaptopurine and a glutamine antagonist in children appears promising, but requires further investigation.

Busulfan, desacetylmethylcolchicine (Colcemid) and 6-mercaptopurine in chronic granulocytic leukemia and CB 1348 (chlorambucil) in chronic lymphocytic leukemia are active, but how they will compare with the more conventional x-ray therapy and P^{32} cannot be stated at the present time.

The colchicine analogs are a new class of compounds with therapeutic activity in chronic granulocytic leukemia and for this reason merit further study.

REFERENCES

1. Pearson, O. H.; Eliel, L. P., and Talbot, T. R., Jr.: The Use of ACTH and Cortisone in Neoplastic Disease, Bull. New York Acad. Med. 26:235, 1950.

2. Farber, S.; Schwachman, H.; Toch, R.; Downings, V.; Kennedy, B. H., and Hyde, J.: The Effect of ACTH in Acute Leukemia in Childhood, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, p. 328.

3. Farber, S.; Downing, V.; Schwachman, H.; Toch, R.; Appleton, R.; Heald, F.; King, J. P., and Farion, D.: Action of ACTH and Cortisone in Acute Leukemia; in Proceedings of the Second Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, p. 251.

4. Bernard, J., and Deltour, G.: Les Nouveaux Traitements des leucoses: T.E.P.A.—H. G. T. 41 (myleran)—6-mercaptopurine — β-mercaptoéthylamine; doses très fortes de cortisone, Semaine Hôp. Paris 67:3430, 1953.

5. Hill, J. M., and Vincent, L.: Traitement des leucémies aiguës par la fluoroydrocortisone, Sang 26:269, 1955.

6. Farber, S.; Diamond, L. K.; Mercer, R. D.; Sylvester, R. F., Jr., and Wolff, J. A.: Temporary Remissons in Acute Leukemia in Children Produced by Folic Acid Antagonist, 4-Amino-Pteroylglutamic Acid (Aminopterin), New England J. Med. 238:787, 1948.

7. Stock, C. C.; Biesele, J. J.; Burchenal, J. H.; Karnofsky, D. A.; Moore, A. E., and Sugiura, K.: Folic Acid Analogs and Experimental Tumors, Ann. New York Acad. Sc. 52:1360, 1950.

8. Burchenal, J. H.; Burchenal, J. R.; Kushida, M. N.; Johnston, S. F., and Williams, B. S.: Studies on the Chemotherapy of Leukemia: II. The Effect of 4-Amino-Pteroylglutamic Acid and 4-Amino-N^{10}-Methyl-Pteroylglutamic Acid on Transplanted Mouse Leukemia, Cancer 2:113, 1949.

9. Law, L. W.; Dunn, T. B.; Boyle, P. J., and Miller, J. H.: Observations on the Effect of a Folic Acid Antagonist on Transplantable Lymphoid Leukemias in Mice, J. Nat. Cancer Inst. 10: 179, 1949.

10. Burchenal, J. H., Murphy, M. L., and Tan, C. T. C.: Treatment of Acute Leukemia, Pediatrics, to be published.

11. Burchenal, J. H.; Murphy, M. L.; Ellison, R. R.; Sykes, M. P.; Tan, T. C.; Leone, L. A.; Karnofsky, D. A.; Craver, L. F.; Dargeon, H. W., and Rhoads, C. P.: Clinical Evaluation of a New Antimetabolite, 6-Mercaptopurine, in the Treatment of Leukemia and Allied Diseases, Blood 8: 965, 1953.

12. Murphy, M. L.; Tan, T. C.; Ellison, R. R.; Karnofsky, D. A., and Burchenal, J. H.: Clinical Evaluation of Chloropurine and Thioguanine, Proc. Am. A. Cancer Res. 2:36, 1955.

13. Ellison, R. R.: Management of Acute Leukemia in Adults, M. Clin. North America 40:743, 1956.

14. Hall, B. E.; Richards, M. D.; Willett, F. M., and Feichtmeir, T. V.: Clinical Experience with 6-Mercaptopurine in Human Neoplasia, Ann. New York Acad. Sc. 60:374, 1954.

15. Bartz, Q. R.; Elder, C. C.; Frohardt, R. P.; Fusari, S. A.; Haskell, T. H.; Johannessen, D. W., and Ryder, A.: Azaserine, a New Tumour-Inhibitory Substance: Isolation and Characterization of Azaserine, Nature 173:72, 1954.

16. Dion, H. W.; Fusari, S. A.; Jakubowski, Z. L.; Zora, J. G., and Bartz, Q. R.: 6-Diazo-5-Oxo-L-Norleucine, a New Tumor-Inhibitory Substance: Isolation and Characterization, Proceedings of the 129th Meeting of the American Chemical Society, 13M, Houston, Texas, 1956.

17. Stock, C. C.; Reilly, H. C.; Buckley, S. M.; Clarke, D. A., and Rhoads, C. P.: Azaserine, a New Tumour-Inhibitory Substance: Studies with Crocker Mouse Sarcoma 180, Nature 173:71, 1954.

18. Clarke, D. A.; Philips, F. S.; Stock, C. C.; Elion, G. B., and Hitchings, G. H.: Combined Chemotherapy of Mouse Sarcoma 180 (S-180), Azaserine, and 6-Mercaptopurine, Proceedings of the 125th Meeting of the American Chemical Society, Kansas City, Mo., 1954.

19. Clarke, D. A.; Reilly, H. C., and Stock, C. C.: 6-Diazo-5-Oxo-L-Norleucine, a New Tumor-Inhibitory Substance: Effects on Mouse Sarcoma 180, Proceedings of the 129th Meeting of the American Chemical Society, 12M, Houston, Texas, 1956.

20. Burchenal, J. H.; Murphy, M. L.; Yuceoglu, M., and Horsfall, M.: The Effect of a New Antimetabolite, O-Diazoacetyl-L-Serine, in Mouse Leukemia, Proc. Am. A. Cancer Res. 1:7, 1954.

21. Burchenal, J. H.; Dagg, M. K.; Weigand, L. S., and Stock, C. C.: Chemotherapy of Leukemia: VIII. The Effect of Diazo-Oxo-L-Norleucine and Mercaptopurine on Transplanted Mouse Leukemia, Proc. Soc. Exper. Biol. & Med., to be published.

22. Buchanan, J. M.; Levenberg, B.; Melnick, I., and Hartman, S. C.: The Specific Action of Azaserine on Enzymes Concerned with Purine Biosynthesis, in Henry Ford Hospital International Symposium on The Leukemias: Etiology and Pathophysiology, New York, Academic Press, Inc., 1956.

23. Skipper, H. E.: Effects of 6-Mercaptopurine on Experimental Tumors, Ann. New York Acad. Sc. 60:267, 1954.

24. Skipper, H. E.: Nucleotide Metabolism and Cancer Chemotherapy, in Henry Ford Hospital International Symposium on The Leukemias: Etiology and Pathophysiology, New York, Academic Press, Inc., 1956.

25. Elion, G. B.; Singer, S., and Hitchings, G. H.: Microbiological Effects of 6-Mercaptopurine, Ann. New York Acad. Sc. 60:200, 1954.

26. Law, L. W., Taormina, V., and Boyle, P. J.: Response of Acute Lymphocytic Leukemias to the Purine Antagonist 6-Mercaptopurine, Ann. New York Acad. Sc. 60:244, 1954.

27. Tivey, H.: Prognosis for Survival in the Leukemias of Childhood: Review of Literature and Proposal of Simple Method of Reporting Survival Data for These Diseases, Pediatrics 10:48, 1952.

28. Haut, A.; Altman, S. J.; Cartwright, G. E., and Wintrobe, M. M.: The Influence of Chemotherapy on Survival in Acute Leukemia, Blood 10:875, 1955.

29. Haddow, A., and Timmis, G. M.: Myleran in Chronic Myeloid Leukæmia: Chemical Constitution and Biological Action, Lancet 1:207, 1953.

30. Galton, D. A. G.: Myleran in Chronic Myeloid Leukæmia: Results of Treatment, Lancet 1: 208, 1953.

31. Haddow, A.: Experimental and Clinical Aspects of the Action of Various Carboxylic Acid Derivatives in the Aromatic Nitrogen Mustard Series, in Ciba Foundation Symposium on Leukæmia Research, edited by G. E. W. Wolstenholme and M. P. Cameron, Boston, Little, Brown & Company, 1954, p. 196.

32. Galton, D. A. G.; Israels, L. G.; Nabarro, J. D. N., and Till, M.: Clinical Trials of *p*-(Di-2-Chloroethylamino)-Phenylbutyric Acid (CB 1348) in Malignant Lymphoma, Brit. M. J. 2:1172, 1955.

33. Haut, A.; Altman, S. J.; Cartwright, G. E., and Wintrobe, M. M.: The Use of Myleran in the Treatment of Chronic Myelocytic Leukemia, A. M. A. Arch. Int. Med. 96:451, 1955.

34. Sykes, M. P.; Philips, F. S., and Karnofsky, D. A.: Comparative Therapeutic Activity of the Nitrogen Mustards and Allied Compounds, M. Clin. North America 40:837, 1956.

35. Hall, B. E.; Willett, F. M.; Smyth, J. D., and Feichtmeier, T. V.: Observations on the Use of *p*-(Di-2-Chloroethylamino) Butyric Acid (CB 1348) in the Treatment of Human Neoplastic Disease, presented at the International Congress of Hematology, Boston, 1956.

36. Bouroncle, B. A.; Doan, C. A.; Wiseman, B. K., and Frajola, W. J.: Evaluation of CB 1348 in Hodgkin's Disease and Allied Disorders, A. M. A. Arch. Int. Med. 97:703, 1956.

37. Santavy, F., and Reichstein, T.: Isolierung neuer Stoffe aus den Samen der Herbstzeitlose Colchicum autumnale, L. Substanzen der Herbstzeitlose und ihre Derivate, Helvet. chim. acta 33:1606, 1950.

38. Moeschlin, S.; Meyer, H., and Lichtman, A.: A New Colchocine Derivative (Demecolcin Ciba) as a Cytostatic Agent in Myelogenous Leukæmia, in Ciba Foundation on Leukæmia Research, edited by G. E. W. Wolstenholme and M. P. Cameron, Boston, Little, Brown & Company, 1954, p. 196.

39. Velluz, L., and Muller, G.: La Thiocolchicine, Bull. soc. chim. France p. 755, 1954.

40. Huguenin, R.; Truhaut, R., and Saracino, R.: Preliminary Results of the Use of a Colchicine Derivative, N-Desacetyl-Thiocolchicine, in the Chemotherapy of Cancer, Bull. cancer 42:308, 1955.

Mechanisms of Destruction of Red Cells in Certain Hemolytic Conditions

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Understanding of the natural history of the anemias associated with increased destruction of red cells has been advanced in the past 20 years, as indicated in recent reviews.* In this report the characteristics of the red cell and the sites and mechanisms of hemolysis are considered for normal red cells and for certain hereditary, congenital, and acquired hemolytic conditions. An attempt is made to indicate the significance and limitations of knowledge concerning the hemolytic processes. More complete details concerning the pathologic physiology and, especially, the clinical aspects of hemolytic conditions are found elsewhere.†

I. Normal Red Blood Cells and Effect of Incubation

Characteristics of the Normal Red Cell Compared to Certain Abnormal Forms

The normal red cell is a biconcave disc containing from 32 to 34 gm. of hemoglobin per 100 ml. of packed red cells. The mechanism which holds the red cell in its unique shape has not been defined, but the recent studies of Prankerd and co-workers [15] suggest a possible metabolic mechanism for the maintenance of the shape. When subjected to solutions of increasing degrees of hypotonicity, the red cell imbibes water and increases in volume without an increase in surface area. Accordingly, the shape changes from a biconcave disc to that of a sphere, which is the form having a maximum volume for any given surface. Further swelling results in rupture of the spherical shaped cell, apparently because the surface area of the cell can not be increased at this critical shape, as demonstrated by Castle and Daland.[16] The degree of hemolysis, or osmotic fragility (OF),‡ of red cells, is related causally to the geometric configuration of the cells and not to differences in osmotic behavior. The normal red cells hemolyze over a narrow range of hypotonicity, as shown in the curves of OF in Figure 1.

The abnormally thin flat cell, such as the target cell, has a small thickness in relation to its diameter. It can swell to large degree, i. e., more than 50%, to reach a spherical form and has, therefore, a "decreased" OF. Conversely, a red cell with an abnormal degree of spheroidicity has a large thickness in relation to its diameter. It can swell only to a small degree, such as 20%, to reach the critical spherical form and has an "increased" OF, as shown in Figure 1.

The susceptibility of red cells to hemolysis by trauma can be tested in vitro by rotation

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* References 1-14.

† References 1-14.

‡ The abbreviation OF in this manuscript will refer to the test performed in vitro of the susceptibility to hemolysis by osmotic rupture. The reader is referred elsewhere [17] for details on technique and to Figures 1 and 2.

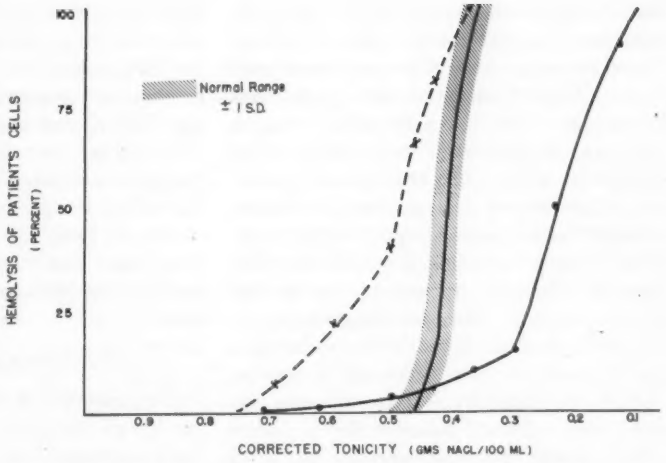

Fig. 1.—Examples of curves of abnormal osmotic fragility in hereditary defects of red cells. The normal range of OF is shown as the mean ± one standard deviation (References 17 and 20). The broken line indicates hereditary spherocytosis with marked increase in OF. The solid line indicates thalassemia major after splenectomy. This shows an extreme span in OF, including a "trail" of red cells with an increased OF. The patient was aged 27, the splenectomy having been performed at age 10.

of samples of blood in contact with glass beads.§

The results may be expressed as the percentage of hemolysis, or the mechanical fragility (MF). It has been shown by Shen and co-workers [18] that the MF is increased by geometric alteration of the red cell, such as spheroidicity, by cohesion of red cells, by changes in the membrane, and by infestation of the red cell with malarial parasites.[19]

Incubation at Body Temperature

Incubation of normal defibrinated blood at body temperature for 24 to 48 hours is accompanied initially by swelling of the red cell, increase in spheroidicity, and increase in OF and MF of the red cells ‖; also, with increase in cell sodium, loss of potassium; with increase in inorganic phosphorus, decrease in organic phosphorus, and, finally, hemolysis. The addition of glucose greatly reduces the hemolysis and appears to protect in part the metabolizing red cell.[22]

Incubation at Four Degrees Centigrade—Storage Lesion

The storage of normal blood at 4 C has

§ References 17-20.

‖ References 17 and 20-22.

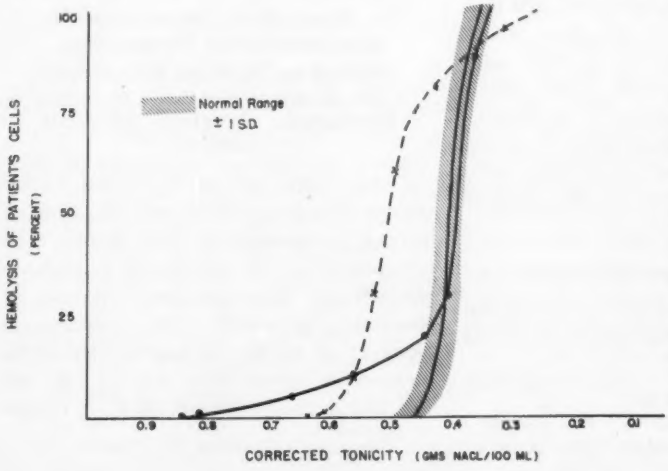

Fig. 2.—Examples of extracorpuscular abnormalities related to increased OF. The broken line indicates acquired hemolytic anemia. The red cells showed a positive antiglobulin (Coombs') test. The solid line indicates drug intoxication from sulfanilamide, resulting in intravascular hemolysis. This patient is reported elsewhere.[1]

been studied extensively under differing conditions ¶ to measure its degree of preservation in terms of survival when transfused in vivo. The red cell deteriorates, or develops a "storage lesion," as indicated by changes that are comparable to those listed in the paragraph above. The changes are greatly slowed but are not prevented by the addition of acid-citrate-dextrose solution to the blood. It is of importance, therefore, that the addition of adenosine to stored blood # will reverse in large part the abnormalities in the red cells that have occurred during a period, such as three weeks of storage at 4 C.[30] As stated by Gabrio and co-workers [30] this evidence indicates that a diminished energy potential appears to be a primary factor in the deterioration of the erythrocyte. Also, the morphology of the red cell has been related, by these observations, to its metabolic homeostasis.

Survival of Normal and Stored Red Cells

The red cells in freshly drawn blood have a maximum survival time of from 100 to 120 days.* Stored blood that has deteriorated may be destroyed so rapidly on the day of transfusion that hemoglobinemia results, or it may be destroyed more slowly over a period of several days.† Well-preserved blood may have a life span of 100 days or longer. Gabrio and co-workers [30] have demonstrated return toward normal for the survival of transfused red cells that had been stored at 4 C for three weeks and then had been treated in vitro with adenosine, with improvement in their physicochemical status. Accordingly, the deterioration as well as improvement of stored blood in vitro have been correlated directly with the length of survival of the red cells in vivo.

Sites and Mechanism of Hemolysis

For the normal red cell it is difficult indeed to determine the mechanism or site of hemolysis. It is likely that abnormal states will lead to an understanding of some of the mechanisms for destruction of normal erythrocytes. For the red cell with a storage lesion, intravascular hemolysis has occurred in some instances with hemoglobinemia associated with red cells with marked increase in OF and MF, as clearly shown in 1942, by Mollison and Young.[24] This blood had been stored for prolonged periods in inadequate preservative solutions.

Significance and Limitations

The relationship of the geometric configuration of the red cell to OF and MF have been emphasized for normal- and abnormal-shaped erythrocytes and for the spheroidicity that occurs on incubation for 24 hours at body temperature and on incubation for several weeks at 4 C in ACD solution. It is emphasized that the red cell, partially deteriorated from prolonged storage, has a shortened life in vivo but may be restored toward normal as observed in vitro and in vivo after adenosine is added in vitro. It is quite likely that the changes occurring at 37 and 4 C are comparable and may represent similar metabolic abnormalities of the red cell. It is emphasized that the increases in spheroidicity, OF, and MF may be related to metabolic changes in the red cell.

II. Examples of Intracorpuscular Abnormalities of Erythrocytes Related to Increased Hemolysis

1. The Spheroidal Red Cell in Hereditary Spherocytosis (Congenital Hemolytic Jaundice)

Characteristics of the Red Cell.—In hereditary spherocytosis the red cells show an increase in spheroidicity, and, therefore, in OF and MF. The amount of hemoglobin per 100 ml. of packed red cells may be abnormally increased.‡ On incubation of blood at 37 C for 24 hours there is an increase in spheroidicity and in OF and MF that is much greater than for normal

¶ References 24-30.
# References 25, 29, and 30.
* References 3, 31, and 32.
† References 24, 27, 28, and 30.
‡ References 1, 17, and 33.

red cells. This has been confirmed by many observers.§ Emerson believes [34] that the abnormal increase in OF on incubation is predictable from the initial spheroidicity of the red cells. His hypothesis does not postulate a defect or alterations in metabolism.

However, Prankerd and co-workers [15] and Motulsky and co-workers [35] report that the erythrocytes in hereditary spherocytosis have abnormal intracellular carbohydrate metabolism. During incubation at 37 C, both groups found some restoration of the changes in OF by the addition of adenosine and glucose. Prankerd and co-workers [15] advanced the hypothesis that adequate availability of energy-rich phosphate bonds may be necessary for the maintenance of the biconcave shape through certain contractile elements in the red cell stroma.

Survival of Red Cells in Hereditary Spherocytosis.—Normal erythrocytes survive normally in the patient with hereditary spherocytosis, but the red cells from the patient are destroyed rapidly in a normal subject.|| However, the abnormal cells from a patient with hereditary spherocytosis have been shown in several instances ¶ to survive normally in a subject whose spleen has been removed. Splenectomy may eliminate the hemolytic anemia, although it does not eliminate the inherent abnormalities of the red cells, which continue for the life of the patient. In some patients, hemolysis continues after splenectomy at a somewhat increased rate.[39]

Sites and Mechanisms of Hemolysis.—There is considerable evidence that the red cells in hereditary spherocytosis are sequestered by the spleen. Emerson and co-workers [17] established that the patient's cells were present in the spleen in high proportion compared to the normal donor's red cells which had been transfused previously. Conversely, Weisman and co-workers [40] showed selective removal in a high degree of hereditary spherocytic red cells by the normal spleen.# Young and co-workers [41] showed selective removal of hereditary spherocytic red cells from a mixture with normal cells when the mixture was used for perfusion after removal of a normal spleen. Sequestration and erythrostasis are both indicated by the observations of Dacie,[42] who was unable to remove all the red cells from the spleen by perfusion in patients with hereditary spherocytosis. Motulsky and co-workers [43] have reported slow mixing times over the spleen when red cells tagged with Cr^{51} were injected into a patient with hereditary spherocytosis. Jandl and co-workers [44] have found rapid sequestration in the spleen of hereditary spherocytic cells tagged with Cr^{51}.

In patients with hereditary spherocytosis, blood from the splenic vein, the pedicle of the spleen, and the splenic pulp showed "conditioning" comparable to the changes seen on incubation at 37 C, with marked increase in spheroidicity, OF, and MF. Normal donor's red cells obtained at the same time from the splenic pulp showed a normal OF and MF.[17]

Evidence that the conditioned cells leave the spleen is provided by their presence in the splenic vein. Some of the more abnormal cells may be reversed toward normal, as indicated by OF and their survival when transfused into a subject without a spleen.[35] Before splenectomy the peripheral blood may show only a trace, or "trail," of red cells with an increased OF, indicating the sequestration of many cells by the spleen with the release of a few conditioned cells. After splenectomy the OF may be significantly increased but show no evidence of selective removal.[17]

Treatment of patients with hereditary spherocytosis with cortisone was observed by Coleman and Finch [45] to reduce the anemia and the OF. It is conceivable that the cortisone decreased the sequestration of red cells by the spleen, although other explanations are possible.

§ References 17 and 20-22.

|| References 3, 36, and 37.

¶ References 17, 35, and 38.

Patient having splenectomy for idiopathic thrombocytopenic purpura but no anemia.

Significance and Limitations.—It is not known why the erythrocyte in hereditary spherocytosis has a defect in shape, possibly an excess of hemoglobin and possibly a defect in carbohydrate metabolism. Studies of the inheritance of this abnormality show Mendelian transmission in most instances, but abnormalities have not been detected in either parent of some otherwise typical cases.[46] Incubation of the red cells from the peripheral blood in vitro at 37 C causes a marked increase in spheroidicity, OF, and MF quite comparable to the changes observed in red cells obtained from the splenic pulp. Adenosine and glucose decrease the changes in OF and MF on incubation at 37 C as they do for normal blood at 4 C.

The intracorpuscular abnormality in hereditary spherocytosis has permitted the study of the above aspects of function of the spleen in a disease without other demonstrable abnormalities of the spleen, of the serum, or of other organs. There is evidence for selection and sequestration of spheroidal red cells by the spleen for erythrostasis, conditioning of red cells, and release by the spleen. However, the mechanisms for selective removal by the spleen of spheroidal cells is not known. It may be related to the abnormal geometric shape of the red cell, as observed by Björkman[47] for starch granules of particular diameter. These appear to be unique and normal functions of the spleen that may not be found elsewhere in the body. Red cells in the spleen may be destroyed by osmotic rupture, but this has not been established. Also some of the blood with increased MF, especially that leaving the spleen, may be destroyed in the periphery.

2. The Abnormal Red Cell in Thalassemia*

Characteristics of the Red Cells.—In the heterozygous trait of thalassemia minor, the red cells are characterized by moderate hypochromia, changes in shape, microcytosis, and stippling. There is no anemia. In the homozygous state of thalassemia major, however, there is severe hypochromic anemia. It is associated with extremely abnormal shapes and sizes of red cells that are predominantly microcytic. An abnormal hemoglobin,† resembling fetal hemoglobin, occurs in large amounts and continues into adult life. The genetic abnormality in thalassemia major appears related to the formation of an abnormal hemoglobin and abnormal forms of red cells. The OF is reported as markedly decreased ‡ and may show a further decrease when the red cells are incubated for 24 hours at body temperatures.[51]

Survival of Red Cells.—The red cells from patients with thalassemia minor have been shown [52] to survive normally in normal recipients, but those from thalassemia major are destroyed at an increased rate.§ When patients with thalassemia major are given transfusions, normal red cells survive normally in many instances.‖ However, the survival was greatly shortened ¶ in some patients, who required multiple transfusions. Certain of these patients were benefited considerably by the removal of a markedly enlarged spleen # and required fewer transfusions.

Sites and Mechanisms of Hemolysis.—In one patient with thalassemia major observed after splenectomy, Weisman and Ham * found a different distribution of red cells than observed in patients before splenectomy. After splenectomy the red cells included spheroidal cells with significantly increased OF as well as the flat cells with decreased OF, which are characteristic of the disease. This is shown in

* The synonyms for thalassemia minor and thalassemia major include Mediterranean trait and Mediterranean anemia, and Cooley's trait and Cooley's anemia.

† References 48 and 49.

‡ References 49 and 51.

§ References 49, 52, and 53.

‖ References 49, 52, and 53.

¶ References 49 and 53.

References 49 and 53.

* Weisman, R., Jr., and Ham, T. H.: Unpublished data.

Figure 1. Harris † has made similar observations in one patient. At the time of splenectomy in an infant aged 2, Weisman and Ham ‡ found that blood from the splenic pulp showed microspherocytes and increased OF and MF. Motulsky and co-workers [43] have shown a slow mixing time in the spleen in thalassemia major. The hypothesis is advanced, therefore, that spheroidal red cells are made in limited number in thalassemia major and may be subject to the same processes of selection, sequestration, erythrostasis, and destruction related to the spleen that have been described above for hereditary spherocytosis. Undoubtedly this mechanism is only a small part of the hemolysis in thalassemia major, since splenectomy brings such limited benefit.

Crosby and Dameshek [54] have observed moderate amounts of free heme pigment in the plasma and hemosiderin in the urine of three patients with severe thalassemia major after splenectomy; none was found in one of these patients who was studied before splenectomy. These data indicate intravascular hemolysis of red cells after splenectomy, possibly related to abnormal forms of red cells, which might have been sequestered previously by the spleen.

Significance and Limitations.—The homozygous abnormality in thalassemia major is associated with a decrease in the adult hemoglobin, an increase of fetal hemoglobin, and the formation of red cells varying in bizarre shapes from spheroidal to target cells and from cells with increased OF and MF to those with markedly decrease OF. The mechanism by which these marked genetic abnormalities occur is unknown. Some destruction of red cells probably occurs in the spleen, and some may occur intravascularly, but much remains to be explained concerning the apparent decreased survival of these cells.

† Harris, J. W.: Unpublished data.

‡ Weisman, R., Jr., and Ham, T. H.: Unpublished data.

3. The Sickle-Shaped Red Cell in the Hemolytic Anemia of Homozygous Sickle-Cell Anemia and Variants of Sickle-Cell Disease

Characteristics of Sickle-Cell Hemoglobin and the Red Cell.—Red cells containing the inherited and abnormal kind of hemoglobin, known as sickle-cell hemoglobin, will change in shape in the test tube from a normal biconcave disc to pointed sickle-shaped forms when the hemoglobin is reduced, as described by Hahn and Gillespie, in 1927.[55] Sickling will occur when the oxygen is removed or a reducing agent such as sodium metabisulfite is used.[56] The discovery in 1949, by Pauling and co-workers,[57] of the different electrophoretic mobility of sickle hemoglobin from that of normal hemoglobin opened the field for study of abnormal hemoglobins and their inheritance. Harris [58] demonstrated that sickle hemoglobin, when freed from stroma and when the oxygen was removed, formed tactoids that appeared like sickled shapes and formed a viscous gel. A critical level of potassium is necessary for the formation of the gel and tactoids.[59] A decrease of the pH of the medium will increase the degree of sickling for a given oxygen tension.[60] Agents that block sulfhydryl groups will inhibit sickling in vitro.[61]

The globin of sickle-cell hemoglobin is the abnormal portion that is responsible for aggregation of molecules. These aggregates deform the red cell about the intracellular tactoids. The change in shape to the sickled form does not increase the OF of the red cells,[62] but the sickled forms have a significant increase in MF resulting from cohesion of the cells.§ In all instances, increasing degrees of sickling are associated with a progressive and significant rise in viscosity of samples of whole blood, as measured in a capillary tube.‖ As shown by Harris and co-workers [62] and by Griggs and Harris,[63] red cells with the heterozygous sickle-cell trait do not sickle at physiologic levels of oxygen unsaturation, so that the

§ References 18 and 62.

‖ References 21 and 62.

sickling process may occur only rarely in vivo. Presumably the difficulty to produce sickling in the body of the patient with sickle-cell trait accounts for the limited clinical manifestations of this abnormality. In sickle-cell anemia, the homozygous abnormality, however, the sickling process occurs readily at physiological levels of oxygen unsaturation of venous blood. Also, irreversibly sickled forms are found in the peripheral blood.[64] To a smaller degree this is true with the variants of sickle-cell-thalassemia disease and sickle-cell-hemoglobin-C disease.[63] There is evidence in sickle-cell anemia and these two variants that sickling and increased viscosity will occur in vivo.

Survival of Red Cells in Sickle-Cell Disease.—The red cells of the sickle-cell trait survive normally, but those of sickle-cell anemia have a short survival time when transfused into normal recipients. Conversely, red cells of normal donors survive normally in most patients with both the sickle-cell trait and sickle-cell anemia. However, Watson and co-workers[65] found an increased rate of destruction of normal donor blood in some patients who had severe sickle-cell anemia and marked splenomegaly. The anemia was markedly reduced after splenectomy.

Sites and Mechanisms of Hemolysis.—It has been demonstrated by Weisman and co-workers[40] that the red cells of sickle-cell trait are not sequestered by a normal spleen, but those of sickle-cell anemia are sequestered to some extent by the patient's spleen or the spleen of a normal subject. The osmotic fragility of the red cells from the pulp of the spleen in sickle-cell anemia shows evidence of conditioning of some of the red cells with marked fragmentation, microspherocytes, and increase in OF and MF.[40] After splenectomy some of the patients showed a greater increase in OF of red cells in the peripheral blood than occurred before splenectomy.[40] These observations, and those of Shen and co-workers,[64] suggest that sickle cells are being conditioned in many parts of the body, probably by erythrostasis. The spleen might then remove some of the spheroidal red cells. In the peripheral blood, Crosby and Dameshek[54] found a minimal increase in heme pigments in the plasma and slight hemosiderinuria in two patients with sickle-cell anemia, indicating a slight degree of intravascular hemolysis.

Capillary thrombi, larger thromboses and infarcts of the spleen and other organs occur in sickle-cell anemia, presumably related to the effect of the sickling process on the viscosity of flow in the capillary bed. Red cells will be destroyed in an infarcted area by mechanisms that are not defined. Jandl[44] has shown considerable sequestration of sickle cells in the liver following the injection of such cells tagged with Cr^{51}.

Significance and Limitations.—The intracorpuscular abnormality in sickle-cell anemia explains intravascular sickling at physiologic levels of venous oxygen. The sickling process explains the increased viscosity of flow in capillary beds that may lead to mechanical destruction of red cells and thromboses. It is postulated that sickling will produce sequestration and erythrostasis of some red cells in many areas of the body, of which the spleen is only one. Further, it is postulated that red cells subject to erythostasis will show increase in spheroidicity, OF, and MF and may hemolyze locally or on recirculation due to increased MF.

Obviously, the limitations of knowledge are great concerning the final mechanisms of hemolysis. The slight anemias of homozygous-hemoglobin-C disease and that of homozygous-hemoglobin-E disease are of unknown cause.¶

4. Production of Spheroidal Erythrocytes by Thermal Injury to the Red Cell

Characteristics of the Red Cell.—The heating of human or dog blood to from 47 C to 65 C produces striking morphologic changes in the erythrocytes.[66] There is progressive subdivision which results in the formation of microcytic particles of red cells,

¶ References 2 and 14.

including spheroidal cells with marked increases in OF and MF. In patients with severe or moderately severe thermal burns, hemoglobinemia and hemoglobinuria occurred regularly. The red cells examined promptly after the burn included a small proportion of spheroidal cells, microspherocytes, and fragmented forms associated with a striking increase in OF and MF of a small part of the population of red cells. Most of the spheroidal red cells disappeared in a period of several hours.

This acute syndrome of hemoglobinemia and hemoglobinuria was reproduced in dogs by heating a sample of a dog's red cells under controlled conditions outside the body and reinjecting them into the same dog without subjecting the animal to heat.[66] In these observations, red cells were rendered spheroidal in vitro and were shown to disappear in a few hours in vivo. In vivo the spheroidal red cells with marked increase in OF and MF were hemolyzed intravascularly. Presumably the destruction could result from mechanical rupture.

The mechanism is not known by which heat, above a critical temperature, produces the progressive and irreversible fragmentation of red cells which results in spheroidicity.

5. Abnormal Red Cells in Paroxysmal Nocturnal Hemoglobinuria

Characteristics of the Red Cell.—Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic hemolytic anemia in which the abnormality is an acquired defect in the red cells. The red cells are susceptible to hemolysis in normal serum.# In vitro, the hemolysis of PNH cells in serum requires properdin, complement, and magnesium, the components of the properdin system.* No known antibody is required, and there is no abnormality in patient's serum which is essential for hemolysis of PNH cells. It is the only naturally † occurring hemolytic system that is known to require properdin. Maximum hemolysis of PNH cells occurs at a pH of approximately 6.8 to 7.0, with decreasing hemolysis at more acid (pH6.5) and more alkaline (pH 7.5) levels. The PNH cells also are more susceptible than normal cells to hemolysis by anti-A and anti-B isoantibodies, but are not hemolyzed by the anti-D isoimmune antibody.

Survival of Red Cells in PNH.—Red cells from normal donors survive normally in patients with PNH, but transfusion of whole blood may be associated with a severe hemolytic episode in which the patient's red cells may be destroyed, apparently by the donor's plasma.‡ This kind of hemolytic transfusion reaction appears to be an exaggeration of the mechanism of hemolysis that goes on at all times in the patient. The reaction can be eliminated by the transfusion of washed cells. Autosurvival studies in patients with PNH,[75] using red cells tagged with Cr,[51] have indicated that the rate of disappearance of the patient's own red cells may vary from extremely rapid to intermediately rapid rates.

Sites and Mechanisms of Hemolysis.—The patient with the highest degree of hemolysis of red cells in vitro showed the most rapid destruction of red cells in vivo and the most marked hemoglobinemia, hemoglobinuria, and reticulocytosis.[75] The patient with the least degree of hemolysis in vitro showed the most moderate rate of destruction of red cells in vivo. There was minimal hemoglobinemia, no hemoglobinuria, hemosiderinuria, and only moderate reticulocytosis. During sleep the degree of intravascular hemolysis and of hemoglobinuria may or may not increase.§ There is no demonstrable relation to the hemolytic system of morphologic abnormality or osmotic or mechanical fragilities.[79] Splenectomy has not given lasting benefit in this disease, and the use of alkali has not been of clinical help.‖

References 3, 67, and 71.

* References 72 and 74.

† Cells treated with tannic acid require the components of the properdin system for hemolysis.[76]

‡ References 3, 75, 77, and 78.

§ References 3 and 67.

‖ References 3 and 67.

Significance and Limitations.—In PNH, the hemolytic system is unique in several ways. The red cells have a corpuscular abnormality, but the patients serum appears to be normal. The origin and the kind of abnormality of the red cell in PNH is not known. The reasons for hemolytic episodes and periods of decreased hemolysis are not known. The abnormality of the red cell is apparently acquired, but no antibody has been demonstrated in the hemolytic system. Hemolysis in vitro requires the properdin system and an optimum pH. It is presumed that hemolysis in vivo is related to the hemolytic system that is demonstrable in vitro.[75]

III. Examples of Extracorpuscular Abnormalities Related to Increased Hemolysis

1. Hemolysins and Agglutinins

Paroxysmal Cold Hemoglobinuria (PCH).—The hemolysin in paroxysmal cold hemoglobinuria will sensitize the human red cell in the cold in the presence of complement.¶ At this stage there is no hemolysis and no agglutination, but the cells are agglutinated by antiglobulin (Coombs') serum.# When these sensitized cells are warmed in the presence of serum complement, hemolysis occurs. In vivo, intravascular hemolysis will occur with chilling and warming of an extremity. The sensitized red cell will be phagocytosed by leucocytes (erythrophagocytosis) in vivo and, also, in vitro in the presence of serum complement.[84]

Hemolytic-Agglutinating Antibodies.—In the ABO system of blood groups, anti-A and anti-B hemolysins occur spontaneously and after isoimmunization. In the presence of serum complement the isohemolysin will hemolyze the red cells for which it is specific. In the absence of complement, the isoantibody will agglutinate the specific red cells. These hemolytic-agglutinating isoantibodies are "complete" antibodies, i. e., they produce agglutination in saline solution.

There are at least three different kinds of clinical situations in vivo in which the hemolytic-agglutinating antibody may be combined with incompatible red cells. In hemolytic transfusion reactions the incompatible cells may be introduced into a recipient who has the antibody, or the antibody may be transfused into a recipient whose red cells are incompatible.[85] Third, the fetal circulation may receive incompatible anti-A or anti-B isoantibodies from the mother.* Following hemolytic transfusion reactions a reproducible series of events may occur, depending on the degree of hemolysis.[95] The incompatible red cells may be destroyed over the course of several days or more rapidly in the period of several hours.† The hemolysis may occur intravenously, as evidenced by hemoglobinemia and hemoglobinuria. Spheroidal red cells with an increased OF and MF may be observed.‡ The spheroidicity and increased OF have persisted for from 8 to 11 days after the injection of incompatible serum without the destruction of these abnormal cells.[89]

Increased spheroidicity and OF with intravascular hemolysis occur regularly with hemolytic-agglutinating antibodies in the following four situations: (1) hemolytic disease of the newborn in man associated with the ABO blood groups §; (2) hemolytic disease of the newborn in dogs in which the antibody is transmitted by the mother's milk to the pups[96]; (3) hemolytic transfusion reactions in dogs due to homologous (canine) antibodies,‖ and (4) from injection of heterologous antibodies made by immunizing one animal against the red cells of another.¶ In a fifth instance, similar results occur with the crystalline protein, concanavalin A, which is derived from the jackbean.[100] It is a hemolytic-agglutinating agent that is not an antibody.[101] Young and

¶ References 80 and 83.

References 82 and 83.

* References 91-94.

† References 85 and 90-92.

‡ References 86, 88, and 89.

§ References 91, 92, and 94.

‖ References 97 and 98.

¶ References 86 and 99.

co-workers # and Swisher and Young [98] have made remarkable contributions by their studies of canine isoantibodies.

Castle, Ham, and Shen [86] observed a severe hemolytic transfusion reaction that was related to an isoagglutinin which was nonhemolytic in vitro. Group A red cells were transfused by error into a patient of Group O. Clumps of agglutinated red cells were observed in the peripheral blood following transfusion. There was hemoglobinemia and hemoglobinuria associated with a marked and transient rise in OF during a period of six hours after transfusion. Within 20 hours no abnormal cells were detectable. The patient recovered. These changes occurred with an anti-A agglutinin that was nonhemolytic in the test tube and were comparable to the changes described above for the hemolytic-agglutinating antibodies.

In vitro the hemolytic-agglutinating sera do not produce any greater spheroidicity or increase in OF of red cells than compatible normal serum when the mixtures are incubated at body temperature.[86] In observations on dogs, red cells incubated with slices of tissue, such as liver, show marked and progressive increases in spheroidicity and OF, possibly due to the effect of tissue factors on red cells.[86] The addition of heterologous (rabbit) anti-dog-red-cell serum to the mixture of dog red cells and liver slices did not increase further the OF of the red cells on incubation. This suggests a nonspecific effect of tissue slices on red cells.[86]

Incomplete Antibodies.—It has been well established that immunization with certain red-cell antigens will result in isoantibodies that will not produce hemolysis in vitro or agglutinate incompatible red cells in saline solutions but will sensitize incompatible red cells as indicated by agglutination in the indirect antiglobulin (Coombs') test. For example, a recipient who is D-negative may be immunized by the transfusion of D-positive blood, or the D-negative female may be immunized by the gestation of a fetus whose blood is D-positive. Subsequent transfusion of D-positive red cells into the immunized recipient may result in a hemolytic transfusion reaction, hemoglobinemia, and hemoglobinuria.* However, there may be no evidence in vitro for a direct-acting hemolytic or agglutinating antibody. Also, there is no spheroidicity of the red cells in vivo and no increased OF and MF.

Mollison and Paterson,[102] in one observation, have shown that D-positive red cells that are sensitized with D-positive antibody in vitro will give up the antibody to the other D-positive red cells when transfused into a normal recipient. The sensitized red cells survived normally, as shown by Jandl.[103] It is apparent that the relatively small amount of antibody is distributed widely in vivo.

In hemolytic disease of the newborn from the anti-D antibody the incomplete antibody can be demonstrated regularly on the red cells of the fetus by the direct antiglobulin (Coombs') test. It can be found in the maternal circulation and usually in excess in the fetal circulation by the indirect antiglobulin (Coombs') test. Thus, the antibody is present on the fetal cells that are destroyed at quite variable rates by a mechanism that can not be reproduced in vitro. Spheroidal red cells and increased OF and MF are not characteristic of the hemolytic process in vivo.[8]

Severe hemolytic transfusion reactions have been demonstrated for several types of isoantibodies that are demonstrable only by the indirect antiglobulin (Coombs') test. Anti-Kell [105] and anti-Duffy [106] antibodies are examples. Remarkably similar results have been observed in dogs with hemolytic transfusion reactions in which incomplete canine antibodies were demonstrable but only after several transfusion reactions.[98]

Acquired Hemolytic Anemia with Hemolysins and Agglutinins.—A wide variety of hemolysins and agglutinins, both complete and incomplete, have been described in acquired hemolytic anemia.† They affect both

References 96 and 97.

* References 3, 7, 8, and 11.

† References 3-5 and 95.

the patient's red cells and normal red cells. It is suspected that these are autoimmune antibodies, but proof is lacking in most instances for the antigen and for the immune process. Specific antibodies are found occasionally.[4] The conditions that affect the degree of hemolysis and agglutination in vitro include variations in pH ‡ and temperature.§ Red cells that show no agglutination in the patient's own serum may be agglutinated by antiglobulin (Coombs') serum, or by suspension in solutions of human or bovine albumin, polyvinylpyrrolidone (P.V.P.), and a variety of large anisometric molecules.

In acquired hemolytic anemia, transfused normal red cells may be sensitized and destroyed at an increased rate.‖ Also the patient's red cells have a shortened survival when observed in the patient. The survival may be shortened when the patient's blood is transfused to a normal recipient.[1] In some instances, but not in all, there may be spheroidal red cells with increased OF and MF (Fig. 2). There may be marked hemoglobinemia and hemoglobinuria in the presence of autohemolysins. Small amounts of heme pigments may occur in the plasma and hemosiderin in the urine of patients with continuing acquired hemolytic anemia, including those who have been treated with steroid hormones and splenectomy.[54]

Sites and Mechanisms of Hemolysis.—Hemolysins, such as the panhemolysins in acquired hemolytic anemia, cold hemolysins (PCH), isohemolysins, hemolytic-agglutinating antibodies, or heterologous anti-red-cell serum, produce hemolysis in vitro and probably in vivo through the hemolytic action of serum complement. None of these antibodies causes any increase over the normal in the OF of red cells in vitro. In vivo, however, the hemolytic-agglutinating antibodies are associated with an additional change in the red cells in many instances, namely, an increase in spheroidicity and in OF and MF which may last for a number of days. Similar observations were made with a nonhemolytic isoagglutinin.

However, in dogs,[98] when the immune antibody is an agglutinin which is nonhemolytic, the canine red cells may survive normally in vivo in spite of being agglutinated in vitro.

When the immune antibody is an incomplete isoantibody, the incompatible red cells may be destroyed rapidly, including intravascular hemolysis, when the cells are introduced into the immunized recipient. This also occurs when a large excess of incompatible antibody is introduced into the patient, such as occurs congenitally in hemolytic disease of the newborn due to anti-D antibody.

Erythrophagocytosis has been observed in the peripheral blood with the cold hemolysin (PCH) and in other conditions, such as acquired hemolytic anemia in human subjects.[111] In dogs, Swisher and Young[98] have demonstrated erythrophagocytosis in the spleen resulting from canine isoantibodies and also from injections of heterologous (rabbit)-anti-dog-red-cell serum.

Significance and Limitations.—For certain hemolytic antibodies the rapid intravascular hemolysis may be explained by direct hemolysis by serum complement. The intravascular hemolysis by incomplete antibodies which may be very rapid at times is not understood, and no in vitro mechanism is demonstrable. It is attractive to speculate that red cells may be sequestered in vivo by agglutination, aggregation,¶ or conglutination[113] in certain tissues or organs, such as the spleen and liver, and be hemolyzed or increased in spheroidicity by tissue factors. Obviously more information is needed to relate the in vivo hemolytic processes that occur clinically with in vitro tests.

2. Hemolytic Anemias Associated with Drugs or Other Chemicals

Changes in Red Cells.—Hemolytic anemia in man and animals has been associated with the administration of certain drugs

‡ References 107 and 108.
§ References 109 and 110.
‖ References 3 and 108.
¶ References 21 and 112.

or chemicals, such as arsine gas,# phenylhydrazine, quinine,[117] and naphthalene,* and in animals with hydroquinone, *p*-aminophenol, and certain other compounds (Fig. 2).[120] In some instances there has been acute hemolytic anemia with hemoglobinemia and hemoglobinuria.[95] The red cells have frequently shown Heinz bodies and, in some instances a change of the hemoglobin to methemoglobin.[121] With some compounds, such as *p*-aminophenol and hydroquinone, it has been possible, in vitro and in vivo, to show increased spheroidicity, increased OF, methemoglobin in the intact red cells, and, eventually, hemolysis.[120] Methemoglobinemia per se is not a cause for increased destruction of red cells.[121]

Dern and co-workers [122] and Beutler [123] have shown a unique susceptibility of the red cells of a limited number of Negroes to destruction by primaquine, acetanilid, sulfanilamide, thiazolsulfone, phenylhydrazine, sulfoxone, and acetophenetidin. The susceptible cells in vitro and in vivo show increased formation of Heinz bodies and a rapid fall in the already low glutathione level.

Drugs, Agglutination, and Hemolysis.—Harris [124] has demonstrated a unique mechanism of hemolysis in a patient who developed hemoglobinemia, hemoglobinuria, spheroidal red cells, with a striking increase in OF and MF, following the treatment of schistosomiasis by the antimony compound stibophen (Fuadin). The patient's cells gave a strong direct antiglobulin (Coombs') test, and also a factor was present in the patient's serum which produced strong agglutination of his own or normal cells, but only in the presence of stibophen. The patient recovered with loss the stibophen-requiring serum factor for red cells when the drug was discontinued.

Freedman and co-workers [125] have described a patient who developed thrombocytopenia and moderately severe hemolytic anemia without evidence for hemoglobinuria while receiving quinidine. The patient's serum contained an antibody for human red cells that required the presence of quinidine to produce agglutination and hemolysis for human red cells. The levoisomer of quinidine was not effective.

Significance and Limitations.—A variety of compounds that produce Heinz bodies in vitro and in vivo may be associated with the development of hemolytic anemia in man and animals.[126] The mechanism is not known. A unique racial susceptibility indicates an important link with glutathione metabolism in the red cell. Certain potential oxidant compounds produce spheroidicity and increased OF as an apparent direct effect on the red cell with alteration of the hemoglobin molecule. The stibophen-requiring-red-cell agglutinin appeared to act, not like an oxidant compound in producing spheroidicity and increased OF and MF of red cells, but like an agglutinin. The quinidine-requiring antibody was both hemolytic and agglutinating. More information is needed concerning the direct effect of certain chemical compounds on the metabolism, the hemoglobin, and the destruction of the red cells.

IV. Hemolytic Anemias of Undetermined Mechanism

There are many instances in which increased destruction of red cells appears as a concomitant, or "secondary," manifestation for which no demonstrable mechanism is known to explain the hemolysis.† Frequently the rate of destruction is moderate in degree, but rarely it may be extreme, with intravascular hemolysis and hemoglobinuria. These hemolytic conditions of undetermined mechanism occur in some patients with the following conditions: cirrhosis of the liver, renal disease and azotemia, lupus erythematosis disseminatus, the collagen diseases, lymphomatous disease, metastatic carcinoma, pernicious anemia, favism, agnogenic myeloid metaplasia, and others. The mechanisms of destruction of

References 114-116.

* References 118 and 119.

† References 3, 5, 12, and 127.

red cells is unknown in hereditary nonspherocytic hemolytic anemia ‡ and in the intravascular hemolysis of exercise.[95] In splenomegaly from unknown causes there may be evidence for increased destruction of red cells.

In thrombotic thrombocytopenic purpura, for example, there may be intravascular hemolysis of the patient's cells, rapid destruction of donor's cells, hemoglobinemia, and hemoglobinuria. No sensitization of the red cells nor serum antibodies have been found, but fragmented red cells have been demonstrated in the peripheral blood.[130] Weisman and co-workers § have confirmed this observation and have demonstrated, in the splenic pulp of one patient, red cells showing extreme fragmentation and spheroidal red cells with a marked increase in OF and MF. These extreme changes in the morphology of the erythrocytes are of unknown cause but probably are related to their rapid destruction.

V. Comment and Summary

From the review of clinical examples of hemolytic anemia certain possible mechanisms and sites of hemolysis of red cells can be outlined.

Mechanisms of Hemolysis

Hemolytic Systems Requiring Serum Complement. — Hemolysins that require serum complement for hemolysis in vitro presumably are responsible for intravascular hemolysis. The hemolysins include isohemolysins in transfusion reactions and hemolytic disease of the newborn, the cold hemolysin (PCH), the variety of hemolysins observed in acquired hemolytic anemia, and heterologous-immune-anti-red-cell antibody. The increases in spheroidicity, OF, and MF that occur in some of these systems are not explained but may be related to agglutination and consequent erythrostasis, as suggested elsewhere.[86]

The red cells in paroxysmal nocturnal hemoglobinuria require the components of the properdin system for hemolysis in vitro. Presumably the chronic intravascular hemolysis in this disease is related to the hemolytic mechanism demonstrated in the test tube.

The ultimate action of complement in the hemolytic system is unknown, but there is evidence that it may act as an esterase.[131]

Erythrostasis.—There is increasing evidence that red cells may be subject to erythrostasis in the spleen or in other sites by such processes as sequestration of spheroidal cells in the spleen, by formation of capillary thrombi in the sickling process, or from intravascular agglutination. It is speculated that erythrostasis may lead to a variety of changes in the red cells, although the mechanisms may not be definable at present. First, the sequestered red cell may show increase in spheroidicity, OF, and MF. This may occur especially when red cells are "incubated" in large numbers out of the main stream of plasma flow, as appears to take place in the spleen. In addition it is possible that cells are hemolyzed or may be altered in spheroidicity from erythrostasis and from the effect of tissue factors that are not yet defined.[86] The rapid hemolysis that occurs with incomplete antibodies in vivo is unexplained by mechanisms that can be demonstrated in vitro. It is possible that conglutination and sequestration lead to erythrostasis and hemolysis by unknown mechanisms in many areas, such as the liver.

Similar biochemical and morphologic changes have been observed in red cells incubated for 24 to 48 hours at body temperature, compared to those stored for prolonged periods at 4 C in preservative solutions. The changes include increases in spheroidicity, OF, and MF. Reversibility of these and the biochemical changes has occurred in part by the addition of adenosine. With improvement by adenosine, the survival of red cells has been prolonged in vivo.

Red cells obtained from the pulp of the spleen, in instances of sequestration, have

‡ References 128 and 129.

§ Weisman, R., Jr.: Unpublished data.

shown significant increases in spheroidicity, OF, and MF. These cells have not been studied metabolically. Hypothetically they may be comparable to those incubated in vitro at body temperature, since they are separated from factors that may be required by the cell to maintain its integrity.

Osmotic Fragility.—As indicated above, erythrostasis often leads to marked changes in spheroidicity, and this change is often associated with markedly increased rates of hemolysis. However, the final relation between spheroidicity and destruction of the cell has not been defined. Spheroidal red cells are the characteristic abnormality of hereditary spherocytosis and have been described here in thalassemia major. Spheroidal red cells have been observed in vivo in a variety of conditions, including reactions to hemolytic-agglutinating antibodies, drug intoxication, and thermal injury to red cells.

In instances of thermal injury to red cells, in certain drug intoxications, and in blood stored for prolonged periods, there is intravascular hemolysis associated with extreme increases in spheroidicity, OF, and MF. Also, hemolysis has been produced by the intravenous injection of purified water U. S. P., which presumably rendered the plasma hypotonic.[132] The same mechanism has been demonstrated in the use of purified water for irrigation of the bladder at the time of transurethal resection of the prostate.[132]

Mechanical Fragility.—In many of the above instances red cells would approach the spherical form and presumably would hemolyze readily by being deformed in the circulation by mechanical forces.[18] Increase in mechanical fragility may explain intravascular hemolysis of smaller degree in severe thalassemia major, in acquired hemolytic anemia, from infestation of red cells with malaria,[19] and possibly from changes in the membrane of the erythrocyte.[18] Also agglutination and the sickling process which cause increased MF in vitro may be responsible for destruction of red cells during the flow of blood in vivo.‖

Erythrophagocytosis.—The phagocytosis of red cells by leucocytes in the peripheral blood has been observed in vivo and can be reproduced in vitro in paroxysmal cold hemoglobinuria. It has been observed in vitro in blood samples from patients with acquired hemolytic anemia. Erythrophagocytosis has been clearly demonstrated in the spleen of dogs that were exposed to incompatible red-cell antibodies.

Sites of Hemolysis

Intravascular Hemolysis.—The occurrence of free hemoglobin in the plasma is taken as evidence that red cells have been hemolyzed intravascularly, but it does not indicate the actual site or the mechanism. The free heme pigment may be present in plasma in small amounts over long periods of time associated with hemosiderinuria in certain chronic hemolytic anemias, such as paroxysmal nocturnal hemoglobinuria. Marked hemoglobinemia and hemoglobinuria may occur in a variety of hemolytic conditions and may be associated with renal failure.[95] Intravascular hemolysis may occur from hemolytic systems requiring complement or properdin or from mechanical fragility or erythrophagocytosis.

Spleen.—The spleen appears to be a site for selective removal and sequestration of spheroidal red cells which are increased further in spheroidicity. Some of these conditioned cells are released by the spleen. It is probable that many red cells are destroyed in situ in the spleen, possibly by osmotic forces as only one of the potential mechanisms. Various mechanisms causing erythrostasis may be active in the spleen in addition to geometic alterations of the red cell. These may include agglutination, increases in concentration of red cells and plasma proteins,[103] conglutination, and other processes. Erythrophagocytosis is known to occur. Infarctions occur in the spleen in sickle-cell anemia and some of the variants of sickle-cell disease. Thrombosis is un-

‖ References 18 and 62.

doubtedly associated with destruction of red cells, although the mechanism of hemolysis is not known.

Other Organs.—There is increasing evidence that the liver may be an important site for sequestration and, probably, for hemolysis of red cells. In sickle-cell anemia it is known that capillary or larger thromboses may occur in many sites of the body with hemolysis of the red cells. In the hemoglobinuria resulting from strenuous running, or in march hemoglobinuria, it is quite probable that red cells are destroyed intravascularly in the kidney. The mechanism of hemolysis is not known, but the occurrence of hemoglobinemia has been established.[133]

REFERENCES

1. Castle, W. B.: Pathologic Physiology: Mechanisms of Disease, edited by W. A. Sodeman, Philadelphia, W. B. Saunders Company, 1956, p. 749.

2. Chernoff, A. I.: Medical Progress: The Human Hemoglobins in Health and Disease, New England J. Med. 253:322, 365, and 416, 1955.

3. Dacie, J. V.: The Hæmolytic Anæmias: Congential and Acquired, New York, Grune & Stratton, Inc., 1954, p. 525.

4. Dacie, J. V.: Seminars on the Hemolytic Anemias: The Auto-Immune Haemolytic Anaemias, Am. J. Med. 18:810, 1955.

5. Dameshek, W.: Seminars on the Hemolytic Anemias: Direct and Indirect Indications, Pathogenic Mechanisms and Classifications, Am. J. Med. 18:315, 1955.

6. Itano, H. A.; Bergren, W. R., and Sturgeon, D.: The Abnormal Hemoglobins, Medicine 35: 121, 1956.

7. Jones, A. R.; Diamond, L. K., and Allen, F. H., Jr.: Medical Progress: A Decade of Progress in the Rh Blood-Group System, New England J. Med. 250:283, 1954.

8. Mollison, P. L.: Blood Transfusion in Clinical Medicine, Oxford, England, Blackwell Scientific Publications, 1951.

9. Ponder, E.: Hemoloysis and Related Phenomena, New York, Grune & Stratton, Inc., 1948.

10. Singer, K.: The Pathogenesis of Sickle Cell Anemia: A Review, Am. J. Clin. Path. 21:858, 1951.

11. Soutter, L.; Allen, F. H., Jr., and Emerson, C. P., Jr.: Medical Progress: Blood Grouping, Blood Banking and Blood Transfusion, New England J. Med. 245:367, 410, and 456, 1951.

12. Wasserman, L. R.; Stats, D.; Schwartz, L., and Fudenberg, H.: Symtomatic and Hemopathic Hemolytic Anemia, Am. J. Med. 18:961, 1955.

13. Young, L. E.: Hereditary Spherocytosis, Am. J. Med. 18:486, 1955.

14. Zuelzer, W. W.; Neel, J. V., and Robinson, A. R.: Abnormal Hemoglobins: Progress in Hematology, edited by L. M. Tocantins, New York, Grune & Stratton, Inc., 1956, Vol. 1, p. 91.

15. Prankerd, T. A. J.; Altman, K. I., and Young, L. E.: Abnormalities of Carbohydrate Metabolism of Red Cells in Hereditary Spherocytosis, J. Clin. Invest. 34:1268, 1955.

16. Castle, W. B., and Daland, C. A.: Susceptibility of Mammalian Erythrocytes to Hemolysis with Hypotonic Solutions: A Function of Differences Between Discoidal Volume and Volume of a Sphere of Equal Surface, Arch. Int. Med. 60: 949, 1937.

17. Emerson, C. P., Jr.; Shen, S. C.; Ham, T. H.; Fleming, E. M., and Castle, W. B.: Studies on the Destruction of Red Blood Cells: IX Quantitative Methods for Determining the Osmotic and Mechanical Fragility of Red Cells in the Peripheral Blood and Splenic Pulp; The Mechanism of Increased Hemolysis in Hereditary Spherocytosis (Congenital Hemolytic Jaundice) as Related to the Functions of the Spleen, A. M. A. Arch. Int. Med. 97:1, 1956.

18. Shen, S. C.; Castle, W. B., and Fleming, E. M.: Experimental and Clinical Observations on increased Mechanical Fragility of Erythrocytes, Science 100:387, 1944.

19. Shen, S. C.; Fleming, E. M., and Castle, W. B.: Osmotic and Mechanical Fragilities of Erythrocytes of Monkeys Infected with P. Knowlesi Malaria, Proc. Soc. Exper. Biol. & Med. 63: 419, 1946.

20. Young, L. E.; Izzo, M. J., and Platzer, R. F.: Hereditary Spherocytosis: I. Clinical, Hemotologic and Genetic Features in 28 Cases, with Particular Reference to the Osmotic and Mechanical Fragility of Incubated Erythrocytes, Blood 6: 1073, 1951.

21. Ham, T. H., and Castle, W. B.: Relation of Increased Hypotonic Fragility and of Erythrostasis to the Mechanism of Hemolysis in Certain Anemias, Tr. A. Am. Physicians 55:127, 1940.

22. Selwyn, J. G., and Dacie, J. V.: Autohemolysis and Other Changes Resulting from the Incubation in Vitro of Red Cells from Patients with Congenital Hemolytic Anemia, Blood 9:414, 1954.

23. Solomon, R. Z.; Hald, P. M., and Peters, J. P.: The State of the Inorganic Components of Human Red Blood Cells, J. Biol. Chem. 132:732, 1940.

24. Mollison, P. L., and Young, I. M.: In Vivo Survival in the Human Subject of Transfused Erythrocytes After Storage in Various Preserva-

tive Solutions, Quart. J. Exper. Physiol. 31:359, 1942.

25. Rapoport, S.: Dimensional, Osmotic, and and Chemical Changes of Erythrocytes in Stored Blood: I. Blood Preserved in Sodium Citrate, Neutral, and Acid Citrate-Glucose (ACD) Mixture, J. Clin. Invest. 26:591, 1947.

26. Parpart, A. K.; Lorenz, P. B.; Parpart, E. R.; Gregg, J. R., and Chase, A. M.: The Osmotic Resistance (Fragility) of Human Red Cells, J. Clin. Invest. 26:636, 1947.

27. Ross, J. F.; Finch, C. A.; Peacock, W. C., and Sammons, M. E.: The in Vitro Preservation and Post-Transfusion Survival of Stored Blood, J. Clin. Invest. 26:687, 1947.

28. Gibson, J. G., II; Peacock, W. C.; Evans, R. D.; Sack, T., and Aub, J. C.: The Rate of Post-Transfusion Loss of Non-Viable Stored Human Erythrocytes and the Re-Utilization of Hemoglobin-Derived Radioactive Iron, J. Clin. Invest. 26:739, 1947.

29. Gabrio, B. W.; Stevens, A. R., Jr., and Finch, C. A.: Erythrocyte Preservation: III. The Reversibility of the Storage Lesion, J. Clin. Invest. 33:252, 1954.

30. Gabrio, B. W.; Donohue, D. M., and Finch, C. A.: Erythrocyte Preservation: V. Relationship Between Chemical Changes and Viability of Stored Blood Treated with Adenosine, J. Clin. Invest. 34:1509, 1955.

31. Strumia, M. M.: The Life Span of Erythrocytes and Their Post-Transfusion Survival: Progress in Hemotology, edited by L. M. Tocantins, New York, Grune & Stratton, Inc., 1956, p. 74.

32. Ebaugh, F. G., Jr.; Emerson, C. P., and Ross, J. F.: The Use Radioactive Chromium 51 as an Erythrocyte Tagging Agent for the Determination of Red Cell Survival in Vivo, J. Clin. Invest. 32:1260, 1953.

33. Sharpsteen, J. R., Jr.: Physico-Chemical Mechanisms in the Pathogenesis of Certain Hemolytic Anemias, Am. J. Med. Sc. 229:506, 1955.

34. Emerson, C. P.: Quantitative Aspects of Osmotic Hemolysis and its Significance in Hereditary Spherocytosis, J. Clin. Invest., to be published.

35. Motulsky, A. G.; Giblett, E.; Coleman, D.; Gabrio, B., and Finch, C. A.: Life Span, Glucose Metabolism and Osmotic Fragility of Erythrocytes in Hereditary Spherocytosis, J. Clin. Invest. 34:911, 1955.

36. Dacie, J. V., and Mollison, P. I.: Survival of Normal Erythrocytes After Transfusion to Patients with Familial Haemolytic Anemia (Acholuric Jaundice), Lancet 1:550, 1943.

37. Kaplan, E., and Zuelzer, W. W.: Erythrocyte Survival Studies in Childhood: I. Methods and General Observations, J. Lab. & Clin. Med. 36:511, 1950.

38. Schrumpf, C. A. A.: Red Cell Survival in Familial Spherocytosis After Splenectomy, Proceedings of the International Society of Hemotology, New York, Grune & Stratton, Inc., 1950, p. 21.

39. Read, R. C.; Wilson, G. W., and Gardner, F. H.: The Use of Radioactive Sodium Chromate to Evaluate the Life Span of the Red Blood Cell in Health and Certain Hemotologic Disorders, Am. J. Med. Sc. 228:40, 1954.

40. Weisman, R., Jr.; Ham, T. H.; Hinz, C. F., Jr., and Harris, J. W.: Studies of the Role of the Spleen in the Destruction of Erythrocytes, Tr. A. Am. Physicians 68:131, 1955.

41. Young, L. E.; Platzer, R. F.; Ervin, D. M., and Izzo, M. J.: Hereditary Spherocytosis: II. Observations on the Role of the Spleen, Blood 6:1099, 1951.

42. Dacie, J. V.: Familial Haemolytic Anemia (Acholuric Jaundice) with Particular Reference to Changes in Fragility Produced by Splenectomy, Quart. J. Med. 36:101, 1943.

43. Motulsky, A. G.; Casserd, F., Giblett, E.: In Vivo Measurement of Splenic Circulation: A Rapid Method for the Demonstration of Splenic Red Cell Sequestration, J. Clin. Invest., to be published.

44. Jandl, J. H.; Greenberg, M. S.; Yonemoto, R. H., and Castle, W. B.: Clinical Determination of the Sites of Red Cell Destruction, Clin. Res. Proc. 3:95, 1955.

45. Coleman, D. H., and Finch, C. A.: Effect of Adrenal Steroids in Hereditary Spherocytic Anemia, J. Lab. & Clin. Med. 47:602, 1956.

46. Young, L. E.: Observations on Inheritance and Heterogeneity of Chronic Spherocytosis, Tr. A. Am. Physicians 68:141, 1955.

47. Björkman, S. E.: The Splenic Circulation with Special Reference to the Function of the Spleen Sinus Wall, Acta med. scandinav. Supp. 191, p. 1, 1947.

48. Notation for Hemoglobin Types and Genes Controlling their Synthesis, Reports and Letters, Science 122:640, 1955.

49. Smith, C. H.; Schulman, I.; Ando, R. E., and Stern, G.: Studies in Mediterranean (Cooley's) Anemia: I. Clinical and Hemotologic Aspects of Splenectomy, with Special Reference to Fetal Hemoglobin Synthesis, Blood 10:582, 1955.

50. Minnich, V.; Na-Nakorn, S.; Chongchareonsuk, S., and Kochaseni, S.: Mediterranean Anemia: A Study of 32 Cases in Thailand, Blood 9:1, 1954.

51. Ham, T. H.; Castle, W. B.; Gardner, F. H., and Daland, G. A.: Medical Progress: Laboratory Diagnosis of Polycythemia and Anemia, New England J. Med. 243:815 and 860, 1950.

52. Kaplan, E., and Zuelzer, W. W.: Erythrocyte Survival Studies in Childhood: II. Studies

in Mediterranean Anemia, J. Lab. & Clin. Med. 36:517, 1950.

53. Lichtman, H. C.; Watson, R. J.; Feldman, F.; Ginsberg, V., and Robinson, J.: Studies on Thalassemia: Part I. An Extracorpuscular Defect in Thalassemia Major; Part II. The Effects of Splenectomy in Thalassemia Major with an Associated Acquired Hemolytic Anemia, J. Clin. Invest. 32:1229, 1953.

54. Crosby, W. H., and Dameshek, W.: The Significance of Hemoglobinemia and Associated Hemosiderinuria, with Particular Reference to Various Types of Hemolytic Anemia, J. Lab. & Clin. Med. 38:829, 1951.

55. Hahn, E. V., and Gillespie, E. B.: Sickle Cell Anemia: Report of a Case Greatly Improved by Splenectomy; Experimental Study of Sickle Cell Formation, Arch. Int. Med. 39:233, 1927.

56. Daland, G. A., and Castle, W. B.: A Simple and Rapid Method for Demonstrating Sickling of Red Blood Cells: The Use of Reducing Agents, J. Lab. & Clin. Med. 33:1082, 1948.

57. Pauling, L.; Itano, H. A.; Singer, S. J., and Wells, I. C.: Sickle Cell Anemia, a Molecular Disease, Science 110:543, 1949.

58. Harris, J. W.: Studies on the Destruction of Red Blood Cells: Molecular Orientation in Sickle Cell Hemoglobin Solutions, Proc. Soc. Exper. Biol. & Med. 75:197, 1950.

59. Griggs, R. C., and Harris, J. W.: The Critical Role of Potassium in the Sickling Phenomenan, Clin. Res. Proc. 4:80, 1956.

60. Greenberg, M. S., and Kass, E. H.: Alkali in the Treatment of Painful Crises in Patients with Sickle Cell Anemia, abstracted, J. Clin. Invest. to be published.

61. Kass, E. H.; Ingbar, S. H.; Harris, J. W., and Ley, A. B.: Chemical Abnormalities in the Erythrocytes in Sickle Cell Anemia, Their Relationship to Sulfhydryl Metabolism and the Effect of ACTH, J. Clin. Invest. 30:653, 1951.

62. Harris, J. W.; Brewster, H. H.; Ham, T. H., and Castle, W. B.: Studies on the Destruction of Red Blood Cells: X. The Biophysics and Biology of Sickle-Cell Disease, Arch. Int. Med. A. M. A. 97:145, 1956.

63. Griggs, R. C. and Harris, J. W.: The Biophysics of the Variants of Sickle-Cell Disease, A. M. A. Arch. Int. Med. 97:315, 1956.

64. Shen, S. C.; Fleming, E. M., and Castle, W. B.: Studies on the Destruction of Red Blood Cells: V. Irreversibly Sickled Erythrocytes; Their Experimental Production in Vitro, Blood 4:498, 1949.

65. Watson, R. J.; Lichtman, H. C., and Shapiro, H. D.: Splenomegaly in Sickle Cell Anemia, Am. J. Med. 20:196, 1956.

66. Ham, T. H.; Shen, S. C.; Fleming, E. M., and Castle, W. B.: Studies on the Destruction of Red Blood Cells: IV. Thermal Injury; Action of Heat in Causing Increased Spheroidicity, Osmotic and Mechanical Fragilities and Hemolysis of Erythrocytes; Observations on the Mechanisms of Destruction of Such Erythrocytes in Dogs and in a Patient with a Fatal Thermal Burn, Blood 3: 373, 1948.

67. Ham, T. H.: Studies on Destruction of Red Blood Cells: I. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria; An Investigation of the Mechanism of Hemolysis, with Observations on 5 Cases, Arch. Int. Med. 64:1271, 1939.

68. Ham, T. H., and Dingle, J. H.: Studies on Destruction of Red Blood Cells: II. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria; Certain Immunological Aspects of the Hemolytic Mechanism with Special Reference to Serum Complement, J. Clin. Invest. 18: 657, 1939.

69. Crosby, W. H., and Dameshek, W.: Paroxysmal Nocturnal Hemoglobinuria: The Mechanism of Hemolysis and Its Relation to the Coagulation Mechanism, Blood 5:822, 1950.

70. Crosby, W. H.: Paroxysmal Nocturnal Hemoglobinuria: Relation of the Clinical Manifestations to Underlying Pathogenic Mechanisms, Blood 8:769, 1953.

71. Crosby, W. H.: Paroxysmal Nocturnal Hemoglobinuria: Plasma Factors of the Hemolytic System, Blood 8:444, 1953.

72. Harris, J. W.; Jordan, W. S.; Pillemer, L., and Desforges, J. F.: The Enzmatic Nature of the Factor in Normal Serum which Hemolyses the Erythrocytes of Paroxysmal Nocturnal Hemoglobinuria, J. Clin. Invest. 30:646, 1951.

73. Pillemer, L.; Blum, L.; Lepow, I. H.; Ross, O. A.; Todd, E. W., and Wardlaw, A. C.: The Properdin System and Immunity: I. Demonstration and Isolation of a New Serum Protein, Properdin, and Its Role in Immune Phenomena, Science 120:279, 1954.

74. Hinz, C. F., Jr.; Jordan, W. S., Jr., and Pillemer, L.: The Properdin System and Immunity: IV. The Hemolysis of Erythrocytes from Patients with Paroxysmal Nocturnal Hemoglobinuria, J. Clin. Invest. 35:453, 1956.

75. Hinz, C. F., Jr.; Weisman, R., Jr., and Hurley, T. H.: Paroxysmal Nocturnal Hemoglobinuria: Relationship of in-Vitro and in-Vivo Hemolysis to Clinical Severity, J. Lab. & Clin. Med., to be published.

76. Hinz, C. F., and Pillemer, L.: The Requirement for the Properdin System in the Hemolysis of Human Erythrocytes Treated with Tannic Acid, J. Clin. Invest. 34:912, 1955.

77. Dacie, J. V., and Mollison, P. L.: Survival of Transfused Erythrocytes from a Donor with Nocturnal Hæmoglobinuria, Lancet 1:390, 1949.

78. Wagley, P. F., and Hickey, M. D.: Susceptibility of Red Cells and Serum Factor in the Mechanism of Hemolysis in Paroxysmal Nocturnal Hemoglobinuria, J. Clin. Invest. 27:559, 1948.

79. Kellermeyer, R. W.: Mechanical Fragility of Erythrocytes from Patients with Paroxysmal Nocturnal Hemoglobinuria, Proc. Soc. Exper. Biol. & Med. 91:157, 1956.

80. Mac Kenzie, G. M.: Paroxysmal Hemoglobinuria: A Review, Medicine 8:159, 1929.

81. Siebens, A. A.; Zinkham, W. H., and Wagley: P. F. Observations on the Mechanism of Hemolysis in Paroxysmal (Cold) Hemoglobinuria, Blood 3:1367, 1948.

82. Jordan, W. S., Jr.; Pillemer, L., and Dingle, J. H.: The Mechanism of Hemolysis in Paroxysmal Cold Hemoglobinuria: I. The Role of Complement and Its Components in the Donath-Landsteiner Reaction, J. Clin. Invest. 30:11, 1951.

83. Jordan, W. S., Jr.; Pillemer, L., and Dingle, J. H.: The Mechanism of Hemolysis in Paroxysmal Cold Hemoglobinuria: II. Observations on the Behavior and Nature of the Antibody, J. Clin. Invest. 30:22, 1951.

84. Jordan, W. S., Jr.; Prouty, R. L.; Heinle, R. W., and Dingle, J. H.: The Mechanism of Hemolysis in Paroxysmal Cold Hemoglobinuria: III. Erythrophagocytosis and Leukopenia, Blood 7:387, 1952.

85. Young, L. E.: Blood Groups and Transfusion Reactions, Combined Staff Clinic, Am. J. Med. 16:878, 1954.

86. Castle, W. B.; Ham, T. H., and Shen, S. C.: Observations on the Mechanism of Hemolytic Transfusion Reactions Occurring Without Demonstrable Hemolysin, Tr. A. Am. Physicians 63: 161, 1950.

87. Ebert, R. V. and Emerson, C. P., Jr.: A Clinical Study of Transfusion Reactions: The Hemolytic Effect of Group-O Blood and Pooled Plasma Containing Incompatible Isoagglutinins, J. Clin. Invest. 25:627, 1946.

88. Ervin, D. M. and Young, L. E.: Dangerous Universal Donors: I. Observations on Destruction of Recipient's A Cells After Transfusion of Group O Blood Contining High Titer of A Antibodies of Immune Type Not Easily Neutralizable by Soluble A Substance, Blood 5:61, 1950.

89. Ervin, D. M.; Christian, R. M., and Young, L. E.: Dangerous Universal Donors: II. Further Observations on in Vivo and in Vitro Behavior of Isoantibodies of Immune Type Present in Group O Blood, Blood 5:553, 1950.

90. Rutsky, J.; Cohen, F., and Zuelzer, W. W.: Anti-A Agglutinins in Pooled Plasma as a Cause of Hemolytic Anemia, Blood 11:403, 1956.

91. Crawford, H.; Cutbush, M., and Mollison, P. L.: Hemolytic Disease of the Newborn Due to Anti-A, Blood 8:620, 1953.

92. Zuelzer, W. W., Kaplan, E.: ABO Heterospecific Pregnancy and Hemolytic Disease: A Study of Normal and Pathologic Variants; IV. Pathologic Variants, A. M. A. Am. J. Dis. Child. 88:319, 1954.

93. Hsia, D. Y., and Gellis, S. S.: Studies on Erythroblastosis Due to ABO Incompatibility, Pediatrics 13:503, 1954.

94. Shumway, C. N.; Miller, G., and Young, L. E.: Hemolytic Disease of the Newborn Due to Anti-A and Anti-B, Pediatrics 15:54, 1955.

95. Ham, T. H.: Hemoglobinuria, Am. J. Med. 18:990, 1955.

96. Young, L. E.; Christian, R. M.; Ervin, D. M.; Davis, R. W.; O'Brien, W. A.; Swisher, S. N., and Yuile, C. L.: Hemolytic Disease in Newborn Dogs, Blood 6:291, 1951.

97. Young, L. E.; Christian, R. M.; Ervin, D. M.; Swisher, S. N.; O'Brien, W. A.; Stewart, W. B., and Yuile, C. L.: Erythrocyte-Isoantibody Reactions in Dogs, Proceedings of the International Society of Hematology, New York, Grune & Stratton, Inc., 1950, p. 226.

98. Swisher, S. N. and Young, L. E.: Studies of the Mechanisms of Erythrocyte Destruction Initiated by Antibodies, Tr. A. Am. Physicians 67:124, 1954.

99. Wasastjerna, C.: Immunohemolytic Mechanisms in Vivo: The Mode of Destruction of Sensitized Red Cells in the Living Organism, Blood 8:1042, 1953.

100. Ham, T. H., and Castle, W. B.: Studies on Destruction of Red Blood Cells: Relation of Increased Hypotonic Fragility and of Erythrostasis to the Mechanism of Hemolysis in Certain Anemias, Proc. Am. Philosoph. Soc. 82:411, 1940.

101. Sumner, J. B., and Howell, S. F.: The Identification of the Hemagglutinin of the Jack Bean with Concanavalin A., J. Bact. 32:227, 1937.

102. Mollison, P. L., and Paterson, J. C. S.: Survival After Transfusion of Rh-Positive Erythrocytes Previously Incubated with Rh Antibody, J. Clin. Path. 2:109, 1949.

103. Jandl, J. H.: Sequestration by the Spleen of Red Cells Sensitized with Incomplete Antibody and with Metallo-Protein Complexes, J. Clin. Invest. 34:912, 1955.

104. Greenwalt, T. J., and Triantaphyllopoulos, D. C.: In Vitro Studies of Red Cell Fragility in Anti-D Hemolytic Disease of the Newborn, J. Lab. & Clin. Med. 45:135, 1955.

105. Ottensooser, F.; Mellone, O., and Biancalana, A.: Fatal Transfusion Reaction Due to the Kell Factor, Blood 8:1029, 1953.

106. Hutcheson, J. B.; Haber, J. M., and Kellner, A.: A Hazard of Repeated Blood Transfusions: Hemolytic Reaction Due to Antibodies to the Duffy (Fy^a) Factor, J. A. M. A. 149:274, 1952.

107. Dacie, J. V.: Hemolysins in Acquired

Hemolytic Anemia: Effect of pH on the Activity in Vitro of a Serum Hemolysin, Blood 4:928, 1949.

108. Gardner, F. H.: Transfer to Normal Red Cells of an Agglutinin Demonstrable in the Acidified Sera of Patients with Acquired Hemolytic Jaundice, J. Clin. Invest. 28:783, 1949.

109. Ham, T. H.; Gardner, F. H.; Wagley, P. F., and Shen, S. C.: Studies on the Mechanism of Hemolytic Anemia and Hemoglobinuria Occurring in Patients with High Concentrations of Serum Cold Agglutinins, J. Clin. Invest. 27:538, 1948.

110. Pisciotta, A. V.: Cold Hemagglutination in Acute and Chronic Hemolytic Syndromes, Blood 10:295, 1955.

111. Zinkham, W. H., and Diamond, L. K.: In Vitro Erythrophagocytosis in Acquired Hemolytic Anemia, Blood 7:592, 1952.

112. Block, E. H.: Microscopic Observations of the Circulating Blood in the Bulbar Conjunctiva in Man in Health and Disease, Ergebn. Anat. 35:1, 1956.

113. Jandl, J. H., and Castle, W. B.: Agglutination on Sensitized Red Cells by Anisometric Molecules, J. Lab. & Clin. Med. 47:669, 1956.

114. Assmann, H.; Bielenstein, H.; Habs, H., and Zu Jeddeloh, B.: Beobachtungen und Untersuchungen bei der Haffkrankheit 1932, Deutche med. Wchnschr. 59:122, 1933.

115. Kiese, M.: Chronische Arsenwasserstoffvergiftung, Arch. exper. Path. u. Pharmakol. 186: 337, 1937.

116. Wilson, R., Jr., and Mangun, G. H.: Acute Hemolytic Anemia in Fertilizer Workers: New Industrial Hazard, South, M. J. 36:212, 1943.

117. Licciardello, A. T., and Stanbury, J. B.: Acute Hemolytic Anemia from Quinine Used as an Abortifacient, New England J. Med. 238:119, 1948.

118. Smillie, W. G.: Betanaphthol Poisoning in the Treatment of Hookworm Disease, J. A. M. A. 74:1503, 1920.

119. Zuelzer, W. W., and Apt, L.: Acute Hemolytic Anemia Due to Naphthalene Poisoning: Clinical and Experimental Study, J. A. M. A. 141: 185, 1949.

120. Emerson, C. P.; Ham, T. H., and Castle, W. B.: Hemolytic Action of Certain Organic Oxidants Derived from Sulfanilamide, Phenylhydrazine and Hydroquinone, J. Clin. Invest. 20: 451, 1941.

121. Finch, C. A.: Medical Progress: Methemoglobinemia and Sulfhemoglobinemia, New England J. Med. 239:470, 1948.

122. Dern, R. J.; Beutler, E., and Alving, A. S.: The Hemolytic Effect of Primaquine: V. Primaquine Sensitivity as a Manifestation of a Multiple Drug Sensitivity, J. Lab. & Clin. Med. 45:30, 1955.

123. Beutler, E.: In Vitro Studies of the Stability of Red Cell Glutathiane: A New Test for Drug Sensitivity, J. Clin. Invest., to be published.

124. Harris, J. W.: Studies on the Mechanism of a Drug-Induced Hemolytic Anemia, J. Lab. Clin. Med. 47:760, 1956.

125. Freedman, A. L.; Ban, P. S., and Brody, E. A.: Hemolytic Anemia Due to Quinidine: Observations on Its Mechanism, Am. J. Med. 20: 806, 1956.

126. Fertman, M. H., and Fertman, M. B.: Toxic Anemias and Heinz Bodies, Medicine 34: 131, 1955.

127. Pritchard, J. A.; Weisman, R., Jr.; Ratnoff, O. D., and Vosburgh, G. J.: Intravascular Hemolysis, Thrombocytopenia and Other Hematologic Abnormalities Associated with Severe Toxemia of Pregnancy, New England J. Med. 250: 89, 1954.

128. Crosby, W. H.: Hereditary Nonspherocytic Hemolytic Anemia, Blood 5:233, 1950.

129. Motulsky, A. G.; Crosby, W. H., and Rappaport, H.: Hereditary Nonspherocytic Hemolytic Disease: A Study of a Singular Familial Hemolytic Syndrome, Blood 9:749, 1954.

130. Adelson, E.; Heitzman, E. J., and Fennessey, J. F.: Thrombohemolytic Thrombocytopenic Purpura, A. M. A. Arch. Int. Med. 94:42, 1954.

131. Lepow, I. H.; Ratnoff, O. D., and Pillemer, L.: Studies on the Pro-Enzymotic Activity of the First Component of Human Complement, J. Clin Invest., to be published.

132. Landsteiner, E. K., and Finch, C. A.: Hemoglobinemia Accompanying Transurethral Resection of the Prostate, New England J. Med. 237:310, 1947.

133. Gilligan, D. R., and Blumgart, H. L.: March Hemoglobinuria: Studies of the Clinical Characteristics, Blood, Metabolism and Mechanism, with Observation on 3 New Cases, and Review of Literature, Medicine 20:341, 1941.

Ventricular Aberration Resulting from Abnormal A-V Nodal Function

XV. Studies on the Mechanism of Ventricular Activity

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The auriculoventricular node usually performs the important function of delaying the auricular impulse in its passage to the ventricles. Direct proof that the site of the delay is at the A-V node has been provided experimentally in this laboratory by Osborne and co-workers.[1] Without this delay the auricles and ventricles would contract practically at the same time, with the resulting decrease in ventricular filling, and the auricles would become functionally useless. When the delaying function of the node is altered, various degrees of block occur, or, on the contrary, conduction through the node becomes accelerated. At the same time, aberrant ventricular complexes of widely varying configuration and timing frequently appear.[2]

Since a knowledge of the relationship between A-V nodal disturbances and various ventricular aberrations appeared important clinically as well as physiologically, experiments were designed to study this relationship more fully. As noted in previous reports,* alteration of nodal function frequently resulted in heart block, accelerated conduction, or nodal arrhythmias. In this study, the observations will be concerned with the aberrant ventricular complexes which occur with abnormal A-V nodal function. Fundamentally, these investigations consisted of interfering with the normal A-V nodal function while recording simultaneous impulses from each ventricle separately by means of strategically placed direct leads.

Four clinical cases are also reported in which A-V nodal dysfunction was associated with a variety of abnormal ventricular complexes. Since the clinical electrocardiographic phenomena in these cases are identical with those produced experimentally by irritating the A-V node, it is suggested that the ventricular aberrations observed in these patients may have resulted from the A-V nodal disorder.

Experimental Data

Material and Methods

Thirty-seven dogs were anesthetized with pentobarbital sodium and the heart exposed in a manner previously described.[4] Ventilation was maintained with a piston-type automatic respirator. Recording electrodes were made of tempered silver wire, 20 mils in diameter, insulated with lacquer except for the tip, which was chlorided. The Sanborn Poly Viso electrocardiograph was used and the tracings recorded at a paper speed of 50 mm. per second. Four simultaneous leads were usually recorded; a direct auricular lead, standard limb lead II, and leads from the right and left side of the interventricular septum or the two ventricular cavities. In many experiments the septal potentials were recorded simultaneously on the Dumont Dual Beam oscillograph.

It was found that the septal and corresponding cavity complexes were almost identical in configuration and timing. Hence, it was possible to determine the onset of depolarization in each ven-

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* References 2 and 3.

tricle by the use of either septal or cavity electrodes. The cavity leads were felt to be superior because the tracings were uncontaminated by injury currents.

The A-V nodal region was located by palpation, using as a landmark the firm ridge formed by that portion of the auriculoventricular junction lying between the tricuspid orifice and the coronary sinus. Exact localization of the node was accomplished by pressing upon portions of this region while observing a continuous tracing. When complete A-V block was noted, it was obvious that the node had been exactly located. This was confirmed when the block disappeared upon releasing the pressure.

Mechanical irritation of the A-V node was accomplished by invaginating the auricular wall and rubbing the nodal tissue with a blunt probe or by inserting the finger into the auricular cavity through a purse-string opening in the right auricular appendage and irritating the nodal tissue directly. These methods were employed in 16 dogs. The results obtained in 10 of these were considered valid. The results in the other six animals were discarded because of the spontaneous occurrence of bundle-branch block or distortion of the tracings by currents of injury, by lack of response to the procedure, or by electrical interference in the recording apparatus.

In four additional animals an attempt was made to visualize and mechanically irritate the nodal region directly by opening the auricle in a bloodless field. In order to accomplish this, the right heart was bypassed, or, in a more acute experiment, the coronary sinus and venae cavae were merely clamped off. In two dogs these efforts were successful. However, the technical difficulties involved in this technique far outweighed the theoretical advantages, and this procedure was discontinued.

In nine dogs as control experiments mechanical stimulation of the A-V node was repeated after permanent, complete A-V block was produced by cutting the bundle of His through the left ventricular wall. In two dogs, the A-V node was severely traumatized with the tip of a probe until complete A-V block appeared. Continuous tracings were recorded until the block disappeared and the electrocardiograms returned to normal.

In six additional animals, chemical alteration of the A-V node was attempted by injecting acetyl strophanthidin into the nodal region, using a previously described technique.[8]

In every experiment the difference in configuration and timing between the right and left septal or cavity deflections was recorded before and during irritation of the A-V nodal region. Normally, depolarization of the left side of the septum begins before depolarization of the right side.[6] As a result, the normal left septal deflection is a Q-S wave and the right septal complex is an RS wave. The intrinsic deflection of the left septal complex occurs slightly earlier than that of the right. Theoretically, abnormally early activation of one ventricle should be manifested by increased negativity in its septum and cavity and increased positivity in the opposite septum and cavity.

Results

1. *Mechanical Irritation of the A-V Node.*—From the 10 experiments, 74 aberrant complexes were chosen for study. Of these, 22 resembled typical complexes of right bundle-branch block (Table 1), 22 simulated left bundle-branch block (Table 2), and the remainder were intermediate in type between normal and complete bundle-branch block (Table 3).

A. Nodal Complexes Simulating Right Bundle-Branch Block and/or Left Ventricular Extrasystoles: In these instances, upon irritating the A-V node, the left ventricle was activated early. The resulting left septal and cavity deflections occurred even earlier relative to the right septal and cavity complexes than they do normally. The difference in time of onset of depolarization of the two sides was considerable, ranging from 10-50 msec., compared to the normal difference of about 3 msec. In these complexes the positive component of the right septal or cavity deflection (which is normally an RS wave) became taller and wider. The ventricular complex in Lead II became aberrant usually with a smaller R wave and deeper S wave. The general picture was that of typical right bundle-branch block (Fig. 1*A*).

B. Nodal Complexes Simulating Left Bundle-Branch Block and/or Right Ventricular Extrasystoles: When the right ventricle was activated earlier than normal there was again a marked difference in the time of onset of depolarization recorded from the right and the left septum and their respective cavities. In these instances the difference ranged from 20-90 msec. The right septal or cavity deflection of all these complexes lost its R wave and became en-

tirely negative. The deflection from the left septum or cavity showed an initial R wave instead of the normal Q-S complex. In Lead II the ventricular complex was usually a tall, wide R-wave. The general picture was characteristic of left bundle-branch block (Fig. 1*B*)

C. Nodal Complexes Simulating Miscel-

TABLE 1.—*Typical Left Side Early**

Complex No.	Time Difference Between L. & Rt. Vent. Activation, Sec.	QRS Amplitude, Mm.						QRS Duration, Sec.
		L. Septum		Rt. Septum		Lead II		
		R	S	R	S	R	S	
1	0.05	0	12	3	2	3	11	0.14
2	0.05	0	12	3	1	3	9	0.12
3	0.05	0	10	4	0	3	13	0.12
4	0.05	0	13	3	0	2	8	0.14
5	0.02	0	7	6	0	3	16	0.14
6	0.03	0	7	6	0	3	16	0.14
7	0.03	0	7	6	0	3	16	0.14
8	0.03	0	7	6	0	3	16	0.14
9	0.02	0	12	6	0	2	17	0.12
10	0.04	0	12	7	0	2	18	0.12
11	0.02	0	25	2	5	13	0	0.08
12	0.03	0	26	2	12	9	3	0.12
13	0.04	0	24	3	14	10	2	0.10
14	0.04	0	23	3	3	14	0	0.10
15	0.01	0	11	4	11	16	4	0.10
16	0.04	0	19	5	8	4	6	0.10
17	0.04	0	14	4	1	2	10	0.08
18	0.04	0	13	5	1	1	11	0.10
19	0.04	0	14	4	1	0	11	0.10
20	0.05	0	14	4	2	1	8	0.10
21	0.05	0	15	3	1	1	8	0.10
22	0.05	0	20	10	19	6	12	0.12
Mean	0.037							

* This Table lists 22 aberrant ventricular complexes where the left ventricle was activated from 20–50 msec. earlier than the right ventricle. The configuration of the left septal complexes is purely negative, while that of the right showed increased positivity. In Lead II there was wide RS configuration, and the general picture is one of right "bundle-branch block." There is no overlapping in characteristics of these complexes, either in timing or in configuration with those of normal complexes. In abnormal complexes, the time difference in activation between left and right ventricles is 20–50 msec., whereas normally the left is activated only approximately 3 msec. earlier than the right. The QRS complex is wider than normal.

TABLE 2.—*Typical Right Side Early**

Complex No.	Time Difference Between Rt. & L. Vent. Activation, Sec.	QRS Amplitude, Mm.						QRS Duration, Sec.
		Rt. Septum		L. Septum		Lead II		
		R	S	R	S	R	S	
1	0.08	0	5	2	4	24	0	0.16
2	0.08	0	5	2	4	23	0	0.18
3	0.08	0	6	2	6	26	0	0.16
4	0.08	0	4	2	4	22	0	0.18
5	0.07	0	6	2	5	22	0	0.18
6	0.08	0	4	2	4	22	0	0.16
7	0.06	0	5	2	4	27	0	0.16
8	0.09	0	5	2	4	21	0	0.16
9	0.08	0	5	2	3	20	0	0.12
10	0.08	0	6	2	5	24	0	0.16
11	0.07	0	4	2	3	21	0	0.16
12	0.08	0	4	2	4	21	0	0.14
13	0.04	0	5	0.5	7	10	0.5	0.10
14	0.04	0	5	0.5	7	13	0	0.12
15	0.02	0	6	1	6	25	0	0.10
16	0.06	0	10	5	3	19	0	0.12
17	0.04	0	28	9	13	26	0	0.14
18	0.04	0	6	6	2	11	0	0.12
19	0.03	0	4	1	6	9	0	0.10
20	0.04	0	5	4	4	9	0	0.10
21	0.04	0	7	4	3	10	0	0.12
22	0.07	0	31	8	6	23	0	0.12
Mean	0.062							

* This Table lists 22 aberrant ventricular complexes where the right ventricle was activated from 20–90 msec. earlier than the left ventricle. The right septal complexes became purely negative, while the left develops an initial positivity. Lead II configuration is a wide RS, and the general picture is that of left "bundle-branch block." Again, as in Table 1, there is no overlapping in characteristics of these abnormal complexes with normal complexes.

TABLE 3.—*Atypical Forms**

Complex No.	Time Difference Between L. & Rt. Vent. Activation, Sec.	QRS Amplitude, Mm.						QRS Duration, Sec.
		L. Septum		Rt. Septum		Lead II		
		R	S	R	S	R	S	
	Left early by							
1	0.02	0	9	0.5	7	12	1	0.08
2	0.02	0	8	0.5	3	12	1	0.08
3	0.00	0.5	20	3	14	28	2	0.08
4	0.03	4	10	4	11	11	6	0.12
5	0.03	5	11	9	11	10	5	0.12
6	0.00	0	16	2	13	27	3	0.08
7	0.01	0.5	13	3	10	12	5	0.08
8	0.01	0.5	13	3	10	12	5	0.08
9	0.00	2	11	2	8	14	0	0.10
10	0.02	0	15	2	12	19	0	0.10
11	0.02	0	9	3	4	13	5	0.14
12	0.01	0	8	3	4	14	7	0.08
13	0.03	0	17	1	11	7	1	0.10
	Right early by							
14	0.01	0	21	0	20	4	5	0.10
15	0.01	0	21	0	19	3	8	0.10
16	0.03	0	8	0	3	8	0	0.08
17	0.01	0	21	1	20	13	1	0.06
18	0.01	2	11	3	8	15	0	0.12
19	0.02	3	9	4	1	7	3	0.10

* This Table lists aberrant ventricular complexes intermediate in form between normal and typical "bundle-branch block" complexes. These complexes do not follow any pattern of typical types; aberration is not as marked, time differences in ventricular activation are not as pronounced, and QRS configuration in Lead II is inconsistent and difficult to classify. These beats are definitely aberrant in one way or another but cannot be grouped with either the typical left "bundle-branch block" (Table 2) or typical right "bundle-branch block" (Table 1) complexes.

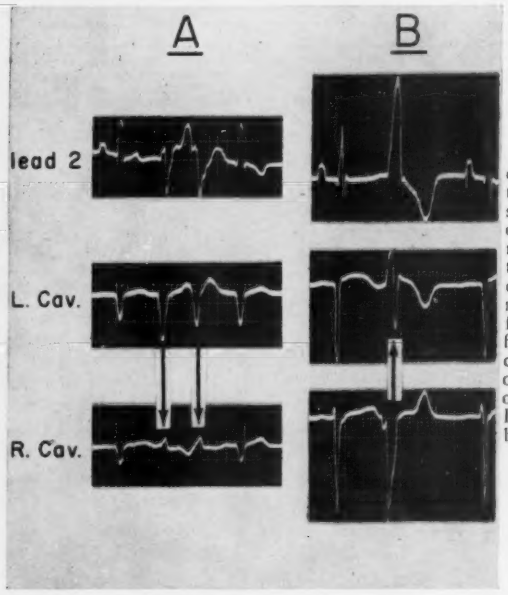

Fig. 1.—Aberrant ventricular depolarization produced by mechanical stimulation of A-V junctional tissue. Simultaneous leads taken at ECG paper speed of 50 mm/second. Arrows indicate direction of impulse. *A*, the intrinsic deflection of the aberrant left septal complex occurs earlier than that of the right. There is more negativity in the left septal complex, more positivity in the right. The corresponding Lead II complex is similar to that found in bundle-branch block. *B*, the intrinsic deflection of the aberrant right septal complex occurs earlier than that of the left. The negativity of the right septal complex is increased, while that of the left shows an initial positivity. The Lead II complex resembles that found in bundle-branch block.

laneous Forms of Ventricular Aberration: In addition to the complexes typical of right or left bundle-branch block, many other types of aberration were produced by irritating the A-V node. In all instances, there was also electrocardiographic evidence suggesting A-V nodal dysfunction. The ventricular aberrations of this group were not as marked as those seen in typical bundle-branch block. The difference in

timing between the two ventricles was less pronounced and sometimes vanished so that depolarization occurred practically simultaneously in both sides. The ventricular complex of Lead II was often difficult to classify. In these experiments there was no sharp line of demarcation between these atypical complexes and those simulating typical bundle-branch block. Any of these various types of deflections could occur singly (Fig. 2) or in bursts (Fig. 3). Oscilloscopic tracings of both right bundle-branch block and left bundle-branch block complexes may be seen in Figure 5.

2. Mechanical Irritation of the A-V Node with Complete Heart Block.—In the preceding experiments the possibility existed that during mechanical nodal irritation, ventricular tissue might have been inadvertently stimulated. In this event, the observed ventricular aberrations could have been attributed to ectopic ventricular foci rather than to a nodal disturbance. In order to determine whether ventricular tissue actually had been stimulated, a control experiment was performed. This consisted of producing permanent, complete A-V block in nine animals by cutting the bundle of His through the free wall of the left ventricle and then mechanically irritating the A-V node as in previous experiments. In six experiments no ventricular aberrations were observed

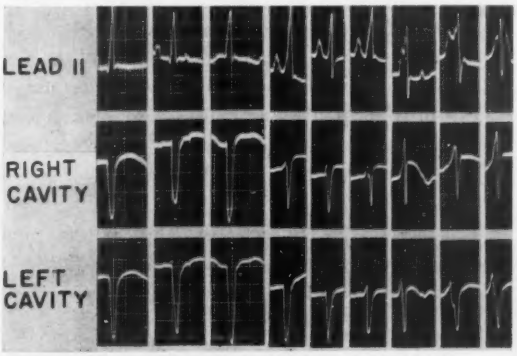

Fig. 2.—Variations in configuration of ventricular complexes in one animal following mechanical irritation of A-V nodal tissue. Simultaneously recorded Lead II and right left cavity leads. Paper speed 50 mm/second.

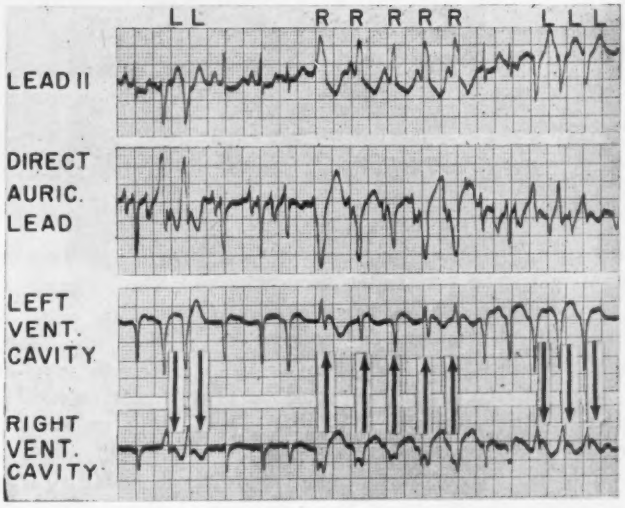

Fig. 3.—Alternation of early left (*L*) and right (*R*) ventricular activation resulting from mechanical stimulation of the A-V nodal region. Four simultaneous leads, paper speed 50 mm/second. In the first burst of aberrant complexes (*LL*), the left cavity complexes are deeper and there is more positivity in the right cavity deflections than in the normal complexes. In Lead II the aberrant ventricular complexes are suggestive of right bundle-branch block. In the second burst (*RRRRR*), the Lead II complexes are tall, R waves are wide, and the P-R intervals are shortened and variable. The general picture is that of left bundle-branch block. The third burst (*LLL*) again shows early left ventricular activation. The electrocardiographic pattern is that of right bundle-branch block.

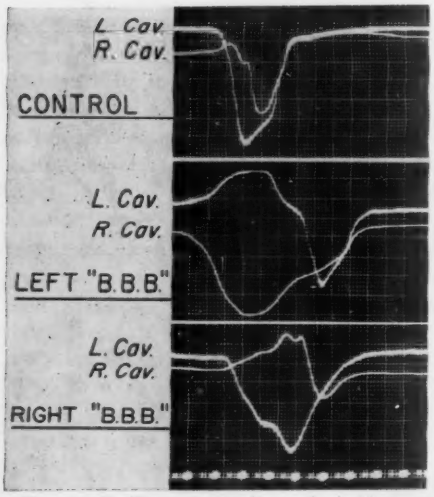

Fig. 4.—Oscilloscopic tracings of simultaneous right and left septal leads taken during mechanical stimulation of A-V nodal region. Top tracing is control taken before stimulation. Middle tracing shows early right ventricular depolarization (Left "BBB"), and bottom tracings show early left ventricular depolarization (Right "BBB"). Time marks at bottom of illustration represent 1/120 second.

tions and strongly suggest that the aberrant complexes must have been due to nodal irritation.

In two dogs, the A-V node was severely traumatized with the tip of a probe until complete A-V block appeared. With the onset of A-V block, various aberrant ventricular responses occurred. These consisted of abnormal complexes of different configurations, ranging from RS waves to tall, wide R waves (Fig. 5). These deflections varied in appearance from almost normal to typical bundle-branch block complexes. Sometimes coupling of left bundle-branch-block or right bundle-branch-block beats with normal-appearing beats was observed (Fig. 6). During a period of 10-15 minutes, complete A-V block subsided and was replaced by partial block. With the disappearance of complete block, about three or four minutes after its onset (but while partial block was still present), the ventricular aberrations also disappeared. There-

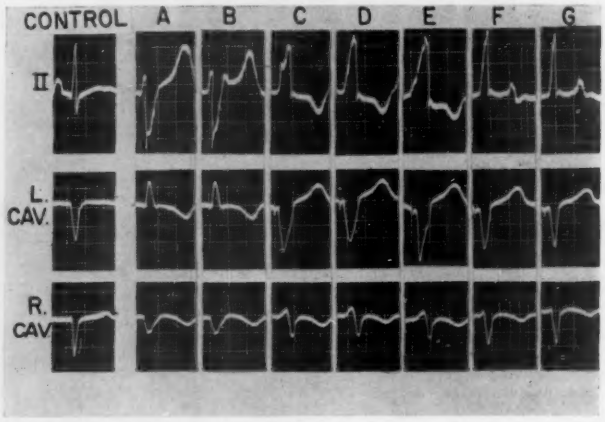

Fig. 5.—Aberrant ventricular complexes of various configurations occurring during acute complete A-V block produced by traumatizing the A-V node. Note the wide variety of aberrations. Simultaneous Lead II and left and right cavity leads. Taken at paper speed of 50 mm/second.

at all. In only three of the nine dogs a rare right ventricular extrasystole occurred. No left ventricular extrasystoles were observed in any of the nine dogs, and no other aberrant ventricular complexes, arrhythmias, or changes in ventricular rate could be produced by irritating the A-V node. These results indicate that direct ventricular stimulation was a negligible factor in producing ventricular aberrations in these investiga-

after, only normal complexes were observed. This sequence of events strongly suggests that the aberrations in the ventricular complex had origin in A-V nodal tissue and were the immediate result of the A-V nodal disturbance. These experimental findings may explain the analogous clinical situation in which acute, complete A-V block is associated with aberrant ventricular complexes of varying types. This picture is not

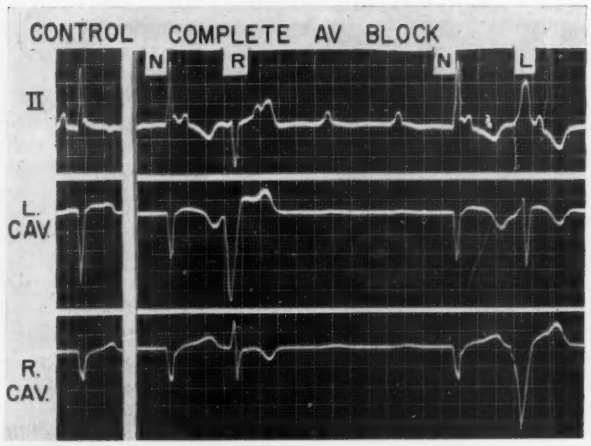

Fig. 6.—Occurrence of both right "bundle-branch block" (*R*) and left "bundle branch block" (*L*) coupled with normal appearing complexes (*N*) following acute, complete A-V block produced by traumatizing the A-V node. Simultaneous Lead II and left and right cavity leads recorded at paper speed of 50 mm/second.

infrequently observed after acute posterior myocardial infarction.

3. *Chemical Irritation of the A-V Node with Resulting Bidirectional Tachycardia.*—Acetyl strophanthidin was injected into the A-V nodal region of six dogs. Two of these animals developed a bidirectional arrhythmia. When the aberrant ventricular complexes became progressively lower in amplitude, the tracing was indistinguishable from bidirectional ventricular tachycardia. Tracings from one of these animals are presented in Figure 7. The development of a bidirectional tachycardia in these animals following injection of the drug was of short duration. It was not possible therefore to prove the nodal origin of this arrhythmia by cutting the bundle of His. Hence it is merely suggested that the aberration resulted from the nodal disturbance rather than from ventricular foci.

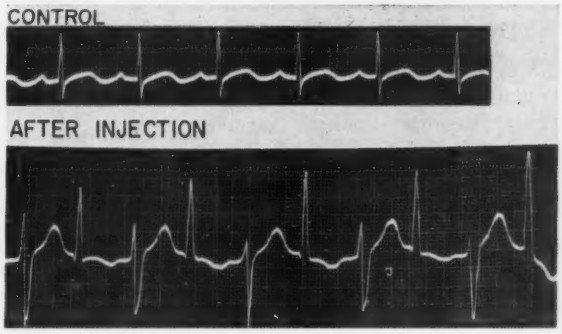

Fig. 7.—Top tracing, control. Lead II, rate 136/minute. QRS, 0.035 second. Bottom tracing, after injection of acetyl strophanthidin in region of A-V node. Lead II. Bidirectional ventricular complexes. Ventricular rate 194/minute, QRS, 0.06 second. Recorded at paper speed of 50 mm/second. Note the resemblance to bidirectional ventricular tachycardia.

Clinical Data

In the experimental portion of this paper, it has been demonstrated that irritation of the A-V node gives rise to a great variety of ventricular aberrations. In clinical instances where a diagnosis is made of ventricular extrasystoles, bundle-branch block, or ventricular tachycardia (including the bidirectional type) and where there is evidence of A-V nodal dysfunction, it is suggested that a single lesion in the A-V node might be responsible for the aberrant clinical complexes. In each of the four clinical cases which follow, an acute disorder of the A-V node was obviously present. In each case one or more of the various types of ventricular aberrations also occurred. It would appear that in these cases a nodal disturbance which was plainly evident might be responsible for the aberrant ventricular complexes and all the abnormalities would become

explicable on the basis of a single lesion instead of assuming multiple lesions.

CASE 1.†—A 72-year-old white woman was admitted to the hospital because of advanced congestive heart failure. The patient became well compensated with digitalization and sodium restriction. The final diagnosis was rheumatic heart disease with aortic stenosis. The past medical history disclosed that previously she had had hyperthyroidism with congestive heart failure. At that time she showed at different intervals auricular tachycardia, auricular flutter, and auricular fibrillation. She had been successfully treated with radioactive iodine and remained relatively asymptomatic until the onset of the present symptoms of heart failure. Figure 8 shows the electrocardiogram recorded during the present admission. Complete heart block was present as demonstrated in the top tracing. The narrow ventricular complexes are apparently of nodal origin, indicating that the complete heart block is also of nodal origin. In the lower tracing, individual complexes are shown from the continuous run of lead aV_F. The QRS complexes varied from a small, broad RS complex to a narrow, completely upright one.

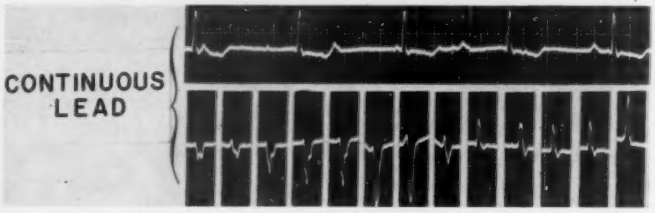

Fig. 8 (Case 1)—Complete heart block in a patient with aortic stenosis. Continuous lead aV_F; the top tracing is uninterrupted portion, and the bottom row consists of selected ventricular complexes to illustrate the variations in configuration which occurred throughout the record.

Summary.—A patient with rheumatic aortic stenosis developed complete heart block. During the brief interval of recording one lead of the electrocardiogram, there is an extreme variation in the configuration of the QRS complex, indicating both early left and right ventricular activation. We have noted several patients with aortic stenosis who manifested electrocardiographic evidence of similar nodal dysfunction.

CASE 2‡—A 50-year-old man was admitted to the hospital with a history of several myocardial infarcts and complete heart block with syncopal attacks. Serial electrocardiograms taken over a period of four days each revealed complete A-V block. Numerous different forms of aberrant ventricular complexes were observed. Examples of these are shown in Figure 9. The first complex illustrated appears to be of nodal origin. The others resemble typical and atypical left-bundle-branch-block and right-bundle-branch-block complexes. Here again, as in Case 1, a distinct nodal disturbance is associated with ventricular aberrations of markedly differing configurations, apparently arising at various times in many different portions of both ventricles. Here also there is a strong similarity to the results obtained experimentally in animals by irritating the A-V node.

Summary.—A patient with complete heart block following myocardial infarction presented at various times ventricular aberrations simulating left bundle-branch block, right bundle-branch block, atypical forms of bundle-branch block, and nodal beats. The usual explanation of the mechanism of such a case would assume the presence of not only a nodal lesion but also many other separate lesions scattered throughout both ventricles, appearing and disappearing at various times. It appears more reasonable to believe that these aberrations resulted from the nodal lesion than from multiple independent lesions in both ventricles.

CASE 3.—A 69-year-old white woman had been treated and followed for seven years in the outpatient department and in the hospital because of recurrent episodes of congestive heart failure due to arteriosclerotic heart disease. Her last hospital admission was necessitated by the sudden onset of acute left ventricular failure. Electrocardiograms dating back five years had shown the presence of normal sinus rhythm and complete left bundle-branch block. Figure 10*A* shows Lead I from the electrocardiogram taken the day following her last admission. There is complete auriculoventricular block. The ventricular rate is 75 per minute, and there is one extrasystolic beat which retains the configuration of the rhythmic beats. The configuration of all the QRS complexes

† Dr. H. K. Hellerstein of Cleveland City Hospital, gave permission for use of this case.

‡ Dr. R. W. Scott, of Cleveland City Hospital, gave permission for use of this case.

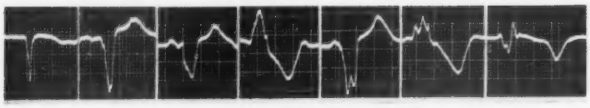

Fig. 9 (Case 2).—Variations in configuration and duration of ventricular complexes of a patient with complete auriculoventricular block. Complexes were selected from serial ECG's over a four-day period. Leads V_5 and V_4.

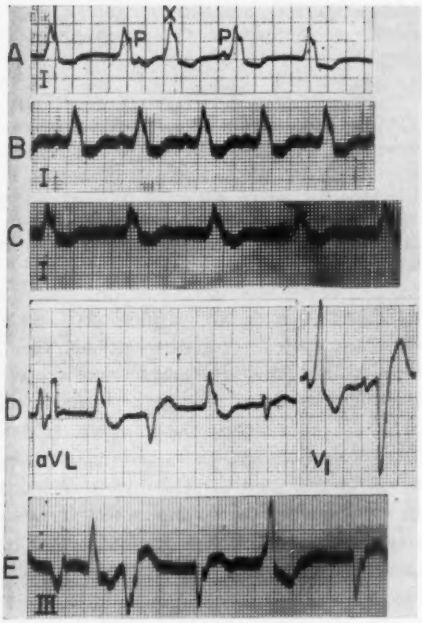

Fig. 10 (Case 3).—*A*, Lead I. Complete auriculoventricular block. There is one "extrasystole" (*X*) which retains the configuration of the rhythmic beats. *B*, Lead I. Two days later. Regular sinus rhythm, rate 88/minute. Pattern of complete left bundle-branch block. P-R interval 0.16 second. QRS 0.16 second. The QRS complex is essentially unchanged from the previous electrocardiogram. *C*, Lead I. One week later. A-V nodal rhythm. Pattern of complete left bundle-branch block. Ventricular rate 68/minute, *D*, Leads aV_L and V_1. Two weeks later. Pattern of complete left bundle-branch block was present. Bidirectional ventricular complexes are observed. There is apparent shortening of the P-R interval with the alteration of the QRS complexes. *E*, Lead III. Three weeks later. A-V nodal rhythm, rate 72/minute. QRS 0.16 second. There are multifocal "ventricular" extrasystoles throughout the record.

suggests a focus in the right ventricle. This was confirmed by precordial leads. Figure 10*B* shows Lead I from the electrocardiogram taken two days later. There is now normal sinus rhythm. The rate is 88 per minute, and there is complete left bundle-branch block. The P-R interval is 0.16 second, and the QRS duration, 0.16 second. The QRS complexes are similar in shape to those of the previous record. Figure 10*C* shows Lead I from the electrocardiogram taken one week later. There is now A-V nodal rhythm and complete left bundle-branch block. The ventricular rate is 68 per minute. Figure 10*D* shows aV_L and V_1 from the electrocardiogram taken two weeks later. At this time there was sinus rhythm with complete left bundle-branch block. In Leads aV_L and V_1 there are bidirectional ventricular complexes. Figure 10*E* shows Lead III from the final electrocardiogram taken three weeks later. All leads taken at this time showed A-V nodal rhythm and complete left bundle-branch block. The rate was 72 per minute, the QRS was 0.16 second in duration. There were several "extrasystoles" apparently arising from different foci.

Summary.—A 69-year-old woman with congestive heart failure displayed at various times numerous dissimilar ventricular aberrations: (*a*) multifocal extrasystoles, (*b*) bundle-branch block, and (*c*) bidirectional complexes. Associated with these various aberrations was a varying nodal disturbance manifested by complete A-V block and later by nodal rhythm. It is of interest that with most of these various disorders of rhythm the QRS complexes are so similar in appearance. With complete A-V block and so-called idioventricular rhythm and ventricular extrasystoles, with bundle-branch block, and with nodal rhythm the ventricular complexes appear to originate in or very near the same focus and might best be explained as manifestations of the A-V nodal disturbance.

CASE 4.—A 25-year-old Negro woman with a long history of alcoholism, malnutrition, Laennec's cirrhosis, and beriberi heart disease had been admitted to the hospital on numerous occasions because of congestive heart failure.

Physical examination disclosed regular sinus rhythm with a rate of 84 per minute. The blood pressure was 120/100. The heart was markedly enlarged, and signs of congestive heart failure were present. Electrocardiograms taken during her 8th and 10th hospital admissions are illustrated in Figure 11. Figure 11*A* shows bidirectional ventricular tachycardia. The rate was 160 per minute. In Figure 11*B* there was complete heart block, with the ventricular complexes apparently arising

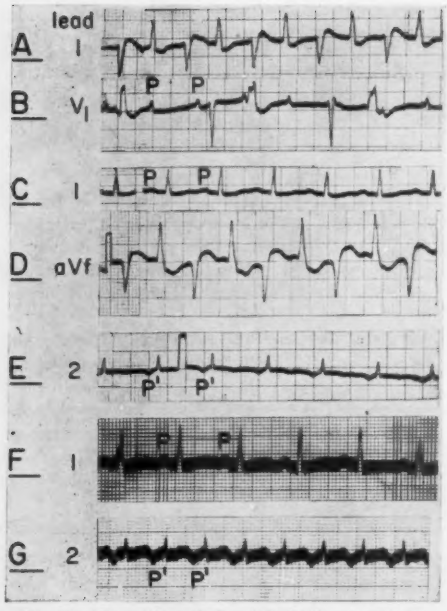

Fig 11 (Case 4).—*A*, Lead I. Bidirectional ventricular tachycardia. Rate 160/minute. QRS, 0.14 second and 0.10 second. *B*, Lead V_1. Immediately following. Complete auriculoventricular block and "idioventricular" rhythm from two foci. The bidirectional ventricular tachycardia disappeared while ECG was being taken. *C*, Lead I. Three days later. Normal sinus rhythm. Rate 115/minute. P-R interval 0.22 second. *D*, Lead aV_F. Immediately following. Bidirectional ventricular tachycardia returned while ECG was being taken. Ventricular rate 160/minute. *E*, Lead II. Two weeks later. There is now upper nodal rhythm at a rate of 100/minute. P-R interval 0.12 second. *F*, Lead I. One month later. Normal sinus rhythm at rate of 96/minute. P-R interval, 0.18 second. *G*, Lead II. Three months later. Paroxysmal tachycardia. Rate 140/minute.

from various foci. The auricular rate was 115 per minute. The "ventricular" foci were discharging at rates of 43 and 45 per minute. Following treatment with procainamide (Pronestyl) there was reversion to sinus rhythm with first-degree heart block. Figure 11*C* shows Lead I from the electrocardiogram taken three days later. The rate was 115 per minute. The P-R interval was 0.22 second. Figure 11*D* is lead aV_F; bidirectional ventricular tachycardia with a rate of 160 per minute was again noted. Figure 11*E* shows Lead II from the electrocardiogram taken two weeks later. There was now upper A-V nodal rhythm. The normal P wave was upright in other leads. The rate was 100 per minute. The P-R interval was 0.12 second. The QRS was of normal duration. Figure 11*F* shows Lead I from the electrocardiogram taken one month later. There was normal sinus rhythm. The rate was 96 per minute. The P-R interval was 0.18 second in duration. Figure 11*G* shows Lead II from the electrocardiogram taken three months later. Paroxysmal tachycardia, probably of upper nodal origin, was now present. The rate was 140 per minute. The QRS was of normal duration.

At various times this patient presented a number of different electrocardiographic phenomena: (*a*) normal sinus rhythm, (*b*) first degree A-V block, (*c*) complete A-V block, (*d*) A-V nodal rhythm, (*e*) nodal paroxysmal tachycardia, (*f*) ventricular beats of various types, and (*g*) bidirectional ventricular tachycardia. Similar ventricular aberrations were produced in dogs by disturbing the A-V node. Of special interest is the close resemblance between the classical bidirectional tachycardia and the same arrhythmia produced experimentally (Fig. 7).

Summary.—This patient at various times presented evidence of varying A-V nodal disorders associated with ventricular beats of different forms and bidirectional ventricular tachycardia. All these phenomena could be explained on the basis of an A-V nodal lesion without the necessity of postulating bizarre and largely unrelated mechanisms. It seems far simpler to envision a single lesion in the node as the responsible factor in such cases than to require at least three separate lesions (one in the node and one in each ventricle) to explain them.

Comment

A series of experimental and clinical observations from this laboratory have indicated that the A-V node, the bundle of His, and the bundle branches constitute a kind of "central nervous system" for the conduction of impulses to the ventricular myocardium. It appeared that specific fibers of the conduction system "supply" specific areas of the ventricular muscle and that cross connections within the system are not physiologically apparent.

It was originally found that irritation of the A-V node may, instead of causing various degrees of block, result in a shortened P-R interval, frequently associated with ventricular aberration.[1] Many of the complexes were indistinguishable from those of the Wolff-Parkinson-White syndrome. The ventricular deflections of these com-

plexes ranged from wide, bizarre waves, like those of typical bundle-branch block, to narrow, normal-looking deflections with intermediate forms of all varieties also observed. Combination of short P-R interval with wide QRS wave was believed to result from accelerated conduction through part of the A-V node. The configuration of the ventricular complexes was believed to be dependent upon the degree of acceleration and the extent of the nodal area involved. It was later found that direct electric current of subthreshold intensity applied to a portion of the A-V node resulted in ventricular aberration of a constant type; stimulation of other parts of the node produced entirely different forms of ventricular complexes. This suggested the extension of fibers (functionally at least) from the node to the periphery, with certain cells in the node invariably terminating in the same ventricular muscle fibers.

Similar conclusions were made by Smith and co-worker,[6] following an experimental study of incomplete bundle-branch block in which distal branches of each main bundle branch were severed. The block thus produced was limited to a well-defined, specific portion of the ipsilateral ventricle as proved by direct leads from the experimental surface. Such instances of segmental bundle-branch block are also seen clinically after some myocardial infarcts.[7] From these observations it again appeared that specific fibers of the conduction system "supply" specific areas of the ventricular muscle and that cross connections within the system are virtually absent in man and dog.

If the concept of a "central nervous system" is applied to the experimental and clinical data reported in the present study, it becomes possible to offer a simple explanation for the findings. For example, irritation of one "side" of the A-V node might cause block in this area. The auricular impulse would, however, pass normally through the unaffected side of the node to its target ventricle. If the block is marked and one side discharges well before the other, the ventricular complexes will assume the form of typical bundle-branch block or extrasystoles of bizarre configuration. If the block is less severe, or slight, atypical forms of ventricular complexes will result. If both sides of the node are irritated simultaneously, a narrow ventricular complex will occur which may or may not be aberrant.

The results of these experiments support the concept of a partial isolation of the fibers of the bundle of His from one another, since a wide range of differences in activation of the two sides of the septum was found during nodal stimulation in the same animal. If the impulse could cross from one fiber to another in the main bundle or from one functional division of the node to another, one might expect that the difference in timing of the septal leads would be much less marked and more constant.

The A-V node lies in close proximity to ventricular muscle. Hence, it might be asked whether, in the course of irritating the A-V node experimentally, ventricular muscle might have been inadvertently stimulated with consequent ventricular aberration. In view of the inability to reproduce the aberrant ventricular complexes when complete heart block is present, this possibility seems highly unlikely. Furthermore, the observation of alternation of right bundle-branch block and left bundle-branch block type complexes in almost successive beats during irritation of a small focus can hardly be explained as a result of infranodal stimulation.

The production of bidirectional tachycardia, apparently ventricular in origin, by chemical alteration of the A-V node is of considerable interest. This unusual arrhythmia was observed as long ago as 1911, by Levy and Lewis,[8] in cats exposed to chloroform, but has rarely been noted experimentally since then. However, its occurrence following the injection of acetyl strophanthidin into the A-V node suggests that it may have resulted from alternating stimulation of each "side" of the node. Such

an explanation, as in the other experimentally produced "ventricular" aberrations, obviates the necessity of postulating the presence of complex mechanisms or multiple ectopic ventricular foci.

Clinical Considerations.—The association of ventricular aberrations of many different types with obvious disorders of the A-V node is not uncommonly observed clinically. The usual interpretation of such findings is that multiple lesions exist not only in the A-V node but also in the ventricles. Such involved explanations may be obviated in view of the results of the present investigation. In cases presenting ventricular aberrations associated with a clear-cut disorder of the A-V node, it is now possible to interpret both abnormalities as a result of the nodal disturbance. Actual proof of such a causal relationship is lacking in clinical cases, but the simplicity of the hypothesis and the experimental evidence presented are highly suggestive.

It is interesting to apply this concept to some unusual clinical phenomena noted in the literature. Carotid sinus stimulation has been reported to result in ventricular tachycardia [9] and also to terminate ventricular tachycardia when present. Ventricular tachycardia has been reported as responding to digitalis.[10] There has been controversy concerning the occurrence of ventricular tachycardia in the Wolff-Parkinson-White syndrome.[11] These observations are more easily reconciled to accepted teachings if one considers that the arrhythmia originated in nodal tissue rather than in the ventricles.

The various clinical ventricular aberrations occurring in association with nodal disturbances are exemplified in the four cases reported in this paper. Their similarity to the experimental findings is striking, and their interpretation as consequences of the nodal disturbance appears to follow logically. When complete heart block is present, various types of aberrant ventricular complexes may occur.

In some cases of complete heart block, especially soon after its onset, there may occur multiple extrasystoles of various bizarre configurations. Such extrasystoles are usually believed to be ventricular in origin, arising from multiple foci. It would appear, however, that a similar picture could result if "extrasystoles" arose in the A-V node and the rate of their conduction through the node and bundle were disturbed in varying degrees. This concept is strongly supported by the occurrence of various bizarre ventricular complexes in dogs with acute heart block produced by traumatizing the A-V node, especially since these aberrations subsided as the node recovered its function.

In other cases with A-V nodal dysfunction, the site of origin of the ventricular complexes may appear to shift from one ventricle to the other. Here again, a similar picture might arise from varying functional alterations of the A-V node, so that conduction through the node and bundle was varied. When the nodal disturbance is severe and discharge occurs at a rapid rate, bidirectional "ventricular" tachycardia may be manifested in the clinical electrocardiogram. This may have been the mechanism in Case 4, in whom nodal dysfunction was evident on numerous occasions and who, at times, also manifested bidirectional ventricular tachycardia. A similar electrocardiogram was reproduced in one of our dogs (Fig. 7) following the injection of acetyl strophanthidin into the region of the A-V node. Bidirectional ventricular tachycardia is occasionally observed clinically and is usually attributed to digitalis intoxication.§ Several theories have been advanced by different observers to explain the mechanism of this arrhythmia. Levy and Lewis [8] suggested that the alternating impulses originated in different ectopic ventricular foci. Some investigators [14] believed that a single focus lying above the bifurcation of the bundle of His was responsible, with the alternating direction of the complexes resulting from alternating conduction down the right and left bundle branches. Gallavardin [15] and later Palmer and White [16] suggested that bidirectional ventricular tachycardia might result from a circus move-

§ References 12 and 13.

ment within the ventricles. Still other theories have been advanced, including parastyoles, reentry, and interference. Scherf and Kisch [17] felt that the arrhythmia could be explained by the presence of a single ectopic ventricular focus associated with a disturbance of intraventricular conduction.

The production of a bidirectional arrhythmia in dogs by introduction of a drug into the node and its occurrence in patients who show evidence of nodal dysfunction suggest that the node alone may be responsible for the abnormal ventricular rhythm. Heart block can occur from lesions of the node or of the bundle of His or both bundle branches; therefore heart block alone does not necessarily mean that the A-V node is diseased as evidenced by nodal rhythms or beats in association with heart block.

In all the cases reported in this paper there was evidence of nodal dysfunction, thus supporting the thesis that the ventricular aberration was of nodal origin. We have also observed cases in which there was no clear-cut evidence of nodal dysfunction (no nodal beats or rhythms) where a nodal origin of the ventricular aberration could be logically accepted without postulating several lesions or multiple ectopic foci. Recently we have seen such a case in a 65-year-old white man with complete heart block. One day he showed ventricular complexes that appeared to arise from the right ventricle; several days later he demonstrated ventricular complexes that appeared to arise from the left ventricle. Ventricular complexes intermediate in form between these two extremes were also recorded. To explain these phenomena, conventional theories would require the existence of multiple areas of disturbance in both the right and left ventricles, shifting in location and often widely separated. But in view of the data presented in this report we must not exclude the possibility of a nodal lesion being responsible for the ventricular aberration. Thus, many instances of alternating right and left bundle-branch block, or "bilateral block," may be explicable on the basis of a nodal disorder.[7]

Summary and Conclusions

It is a well-known clinical observation that ventricular aberrations occur commonly in the presence of A-V nodal disorders. This association has also been noted experimentally. The relationship between disturbances of the node and aberrations of the ventricular complex, however, has not been thoroughly investigated. A series of experiments was therefore designed and carried out in order to clarify the significance and mechanism of this association. Essentially these experiments consisted of interfering with normal nodal function by irritating or traumatizing the A-V node in 36 dogs by mechanical and chemical means and observing what ventricular aberrations, if any, would occur. The ventricular deflections following disturbance of the node were studied by means of strategically placed recording electrodes in each ventricle.

Interference with A-V nodal function resulted in many different types of ventricular aberration. The aberrant ventricular response took the form of complexes resembling typical right bundle-branch block or typical left bundle-branch block and many forms intermediate between these two. It was impossible to classify these intermediate forms as being distinctly characteristic of any specific aberration.

Such ventricular complexes are usually attributed to disturbances in the ventricular muscle itself. In the present experiments, however, it was shown that the actual origin of the ventricular aberrations was a disorder of A-V nodal function.

These results, and data derived from previous studies, strongly suggest that the A-V node and intraventricular conduction system is functionally divided so that specific portions of the node transmit impulses to specific areas of the ventricles.

The form and duration of the aberrant ventricular complexes resulting from A-V nodal dysfunction suggest abnormally early or late depolarization of one ventricle. Their direction and timing depend upon which ventricle is activated first and upon the time

interval between activation of the two ventricles.

Since the A-V node may be conceived to be functionally divided, early activation of one ventricle may be considered to result from accelerated conduction through the homolateral "side" of the node, or from block in the contralateral "side" of the node.

Bidirectional ventricular tachycardia was produced by injecting acetyl strophanthidin into A-V nodal region in two animals. It is suggested that both "sides" of the node were irritated with resulting alternation of impulses down each side.

Some clinical applications have been suggested. Certain cases of Wolff-Parkinson-White syndrome, bundle-branch block, and ventricular extrasystoles may be due to either disease or functional changes in the A-V node. Similarly, it is suggested that in some instances of apparent idioventricular rhythm, multifocal ventricular extrasystoles and unifocal or bidirectional ventricular tachycardia may actually result from A-V nodal dysfunction.

Four clinical cases demonstrating aberrant ventricular depolarization are reported. In each instance there was, in addition to the ventricular aberration, electrocardiographic evidence of A-V nodal dysfunction manifested at least by one of the following: (*a*) complete atrioventricular block, (*b*) A-V nodal rhythm, (*c*) A-V nodal tachycardia, (*d*) abnormal P-R intervals. Bidirectional ventricular tachycardia occurred in one case. The findings in these clinical cases are closely analogous to those observed after experimental interference with A-V nodal function.

It is suggested that some of these disturbances may result from simultaneous disorder of both pacemaking and conduction functions of the A-V node.

The mechanism of such cases may thus be conceived as the consequences of a single lesion in the A-V node, which could account for all the observed ventricular aberrations as well as the nodal dysfunction.

REFERENCES

1. Osborne, J. A.; Corday, E.; Fields, J.; Kennamer, R.; Smith, L. A., and Prinzmetal, M.: Studies on the Mechanism of Ventricular Activity: I. The Nature of the P-R Interval, Am. Heart J. 42:503, 1951.

2. Prinzmetal, M.; Kennamer, R.; Corday, E.; Osborne, J. M.; Fields, J., and Smith, L. A.: Accelerated Conduction: The Wolff-Parkinson-White Syndrome and Related Conditions, New York, Grune & Stratton, Inc., 1952.

3. Borduas, J. L.; Rakita, L.; Kennamer, R., and Prinzmetal, M.: Studies on the Mechanism of Ventricular Activity: XIV. Clinical and Experimental Studies of Accelerated Auriculo-Ventricular Conduction, Circulation 11:69, 1955.

4. Prinzmetal, M.; Corday, E.; Brill, I.; Oblath, R.; Kruger, H.; Fields, J.; Fleig, W.; Goldman, A.; Karpman, H.; Kennamer, S. R.; Osborne, J. A.; Sellers, A. L., and Smith, L. A.: The Auricular Arrhythmias, Springfield, Ill., Charles C Thomas, Publisher, 1952.

5. Wilson, F. N.; Rosenbaum, F. F., and Johnston, F. D.: Interpretation of the Ventricular Complex of the Electrocardiogram, in Advances in Internal Medicine, edited by W. Dock and I. Snapper, New York, Interscience Publishers, Inc., 1947, Vol. 2.

6. Smith, L. A.; Kennamer, R., and Prinzmetal, M.: Studies on the Mechanism of Ventricular Activity: IV. Ventricular Excitation in Segmental and Diffuse Types of Experimental Bundle-Branch Block, Circulation Res. 2:221, 1954.

7. Lepeschkin, E.: Modern Electrocardiography: Vol. I. The P-Q-R-S-T-U Complex, Baltimore; Williams & Wilkins Company, 1951.

8. Levy, A. G., and Lewis, T.: Heart Irregularities, Resulting from Inhalation of Four Percentages of Chloroform Vapour, and Their Relationship to Ventricular Fibrillation, Heart 3:99, 1911.

9. Meredith, H. C., Jr., and Beckwith, J. R.: Development of Ventricular Tachycardia Following Carotid Sinus Stimulation in Paroxysmal Supraventricular Tachycardia, Am. Heart J. 39:604, 1950.

10. Gilson, J. S., and Schemm, F. R.: The Use of Digitalis in Spite of the Presence of Ventricular Tachycardia, Circulation 2:278, 1950.

11. Langendorf, R.; Lev, M., and Pick, R.: Auricular Fibrillation with Anomalous A-V Excitation (WPW Syndrome) Imitating Ventricular Paroxysmal Tachycardia: Case Report with Clinical and Autopsy Findings and Critical Review of Literature, Acta cardiol. 7:241, 1952.

12. Schwensen, C.: Ventricular Tachycardia as a Result of Administration of Digitalis, Heart 9:199, 1922.

13. Felberbaum, D.: Paroxysmal Ventricular Tachycardia: Report of Unusual Type, Am. J. M. Sc. 166:211, 1923.

14. Zimdahl, W. T., and Kramer, L. I.: On the Mechanism of Paroxysmal Tachycardia with Rhythmic Alternation in the Direction of the Ventricular Complexes, Am. Heart J. 33:218, 1947.

15. Gallavardin, L.: Terminal Ventricular Tachycardia, Alternating or Multiform Complexes, Its Relation with Severe Form of Ventricular Extrasystoles, Arch. mal. coeur 19:153, 1926.

16. Palmer, R., and White, P. D.: Paroxysmal Ventricular Tachycardia with Rhythmic Alternation in Direction of the Ventricular Complexes of the Electrocardiogram, Am. Heart J. 3:454, 1928.

17. Scherf, D., and Kisch, F.: Ventricular Tachycardia with Variform Ventricular Complexes, Bull. New York M. Coll. 2:73, 1939.

The Psychosomatic Problem in Drug Evaluation

The Importance of Studying Pharmacodynamics and Establishing Effective Dosage Schedules

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If a new drug is to be studied properly the investigation must be approached systematically. After adequate laboratory observations have been completed, the most important studies required are those related to clinical pharmacodynamics and probable therapeutic applications. It is after these studies have been completed that an attempt should be made to quantitate therapeutic results, utilizing such methods as double-blind studies, and then only in those indications where the drug appears to be of therapeutic value. After all, it is pointless to study a drug, using a double-blind technique or any other method, if initial screening studies indicate that the drug has little or no therapeutic value within a safe, tolerable dosage range.

Double-blind studies are most useful for evaluating the effects of drugs that are only moderately potent and notably when objective tests of therapeutic efficacy are not available. This is particularly true of drugs used by the neuropsychiatrist, since a large part of the evaluation of these agents depends upon subjective rather than objective observations and deductions. By contrast, there is little need for application of the double-blind technique in studying the diuretic effect of meralluride for the treatment of heart failure or penicillin for the treatment of pneumococcic pneumonia. All too often, the double-blind technique is applied before the clinical pharmacology has been completed and before the therapeutic and maximum dosage schedules are determined. If a drug has been studied utilizing a double-blind technique and the study proves negative, this is usually accepted as a factual report. Too often this is not true. It is only when maximum dosage has been determined and individualized for each patient that conclusive deductions can be drawn. This is particularly true of drugs affecting the cardiovascular, the autonomic nervous, and the central nervous systems.

This report concerns the necessity of undertaking studies to determine adequate clinical pharmacology and proper dosage schedules before proceeding to more detailed and complicated techniques. The necessity of ruling out psychosomatic aspects of response to drugs is not denied, but this constitutes only one aspect of proper drug evaluation, and one that is frequently overemphasized by the enthusiastic "therapeutic nihilist." It is as erroneous to conclude that a drug has no therapeutic value before a complete investigation has been carried out as for the "therapeutic enthusiast" to find every drug studied "superior to all previous agents."

Observations and Comment

Drugs which can be used at a relatively Fixed Dose

Drugs should not be studied with a double-blind technique until the clinical pharmacology and dosage requirements have been reasonably well established. When this is done, it will be found that some

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TABLE 1.—*Comparison of Chlormerodrin (Neohydrin) with Simple Placebo Substitution and Double-Blind Technique When Used for the Treatment of Patients with Heart Failure*

	Dose of Placebo and Chlormerodrin					
	2 tablets/day*		4 tablets/day*		8 tablets/day*	
No. patients treated	68		64		69	
	Patients in whom Heart Failure Controlled					
	No.	Per Cent	No.	Per Cent	No.	Per Cent
Controlled with placebo	14	21	14	22	11	16
Controlled with chlormerodrin	17	25	48	75	63	91
Double-blind technique						
Placebo	16	24	16	25	15	22
Chlormerodrin	16	24	46	72	60	87

* Each tablet of Chlormerodrin contained drug in equivalent to 10 mg. of Hg.

drugs can be used in a fixed dosage in the majority of patients, notably such drugs as diuretics in the treatment of heart failure and other diseases where retention of sodium and water occur. While a certain amount of dosage adjustment is necessary to assure that each patient obtains maximum therapeutic benefit with minimal side-effects, a dosage range which will be effective for nearly all patients without producing intolerable side-effects can usually be established for many of these drugs. It is only after this has been done, that it is feasible to evaluate the drug against placebos or by utilization of the double-blind technique.

TABLE 2.—*Comparison of Subjective Response, Objective Response, and Sodium Excretion in Patients with Heart Failure*

	Subjective Improvement		Clinical Objective Improvement		Significant Increase in Sodium Excretion	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
No. patients treated	46	100	46	100	46	100
Placebo response	12	26	4	9	2	4
Chlormerodrin (Neohydrin) (8 tablets)	36	78	40	87	42	91
Double-blind technique						
Placebo	15	33	7	15	3	7
Chlormerodrin	35	76	41	89	43	93

Tables 1 and 2 are examples of the variation that can be obtained in a group of patients treated with diuretics for heart failure. When both subjective manifestations and objective clinical observations were used to evaluate the efficacy of drug therapy, approximately the same degree of effectiveness was obtained with placebo (21%) as with chlormerodrin (Neohydrin) (25%) at the two-tablet dosage level. Interestingly enough, the recommended dose at the time of the study was one to three tablets. The improvement in the patients responding to placebo may have been due partly to a psychogenic response and partly to the fact that they were apparently in minimum heart failure and did not require diuretics routinely. Some remained controlled without further medication. When the dosage was increased to eight tablets per day the degree of effectiveness obtained with the placebo (16%) remained practically unchanged, whereas that obtained with chlormerodrin increased from 25% to 91%. Such findings show that it is only when the diuretic was given in sufficient dosage that it could produce diuresis and subsequent improvement in patients with moderate to severe heart failure. There was very little difference between the ob-

servations employing a simple placebo substitution technique for obtaining control observations and those obtained with a double-blind technique. It is well to emphasize here that the investigators working on this project had extensive experience in evaluating the efficacy of many drugs at the clinical level. Consequently, the study was conducted as a routine chore, since chlormerodrin had already been released for general use.

These observations emphasize the importance of establishing adequate dosage levels before deductions are drawn concerning the therapeutic efficacy of any drug. When subtherapeutic doses are employed, the drug evaluated is actually being used as a placebo, and the investigator places himself in the absurd situation of having evaluated a placebo against an active drug using a placebo dose.

Table 2 emphasizes the importance of using, whenever possible, objective tests for evaluating the therapeutic effects of a drug. It shows the results obtained in a study to determine the effectiveness of a diuretic compared with a placebo when three different methods of judging results were utilized. First, when the patient's subjective response to therapy was evaluated, second, when the clinician evaluated the response to therapy on the basis of physical examination and patient's subjective reports, and third, by the determination of sodium levels in 24-hour urine samples. When subjective information alone was used for evaluation, about 26% of the patients seemed to be well controlled on placebo medication, and about the same incidence of placebo responses occurred (33%) when the double-blind technique was employed. When clinical objective information as well as the

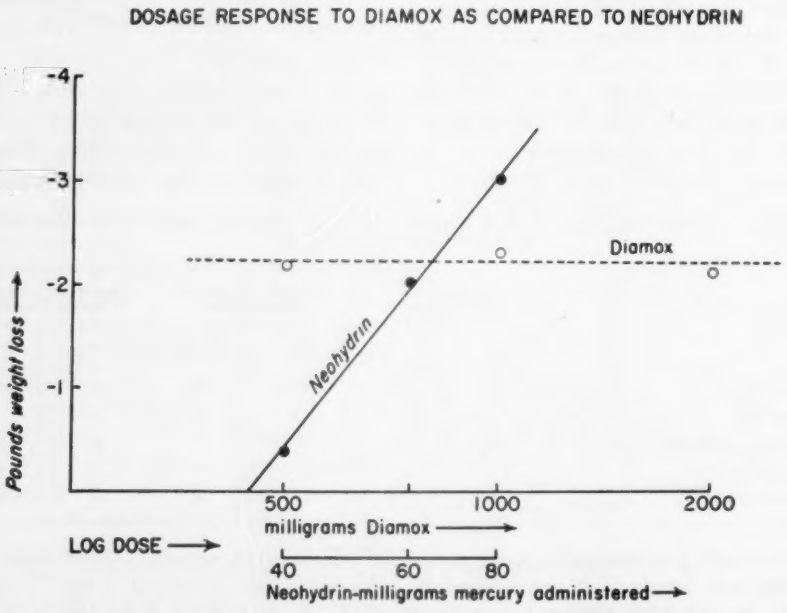

Fig. 1.—This is the acute dosage response curve (two to eight tablets) of chlormerodrin (Neohydrin) as compared to a dose of 500 to 2000 mg. of acetazoleamide (Diamox) when each was used as a diuretic for the treatment of heart failure in the same group of patients. Chlormerodrin in a dose of less than four tablets (equivalent to 40 mg. of Hg) was inactive as a diuretic when compared to 500 mg. of acetazoleamide. However, when the dose of each diuretic was increased, the diuretic potency of chlormerodrin exceeded that of acetazoleamide. Reproduced with permission from Moyer and Hughes, *Journal of Chronic Diseases* 2:678, 1955, The C. V. Mosby Company, St. Louis.

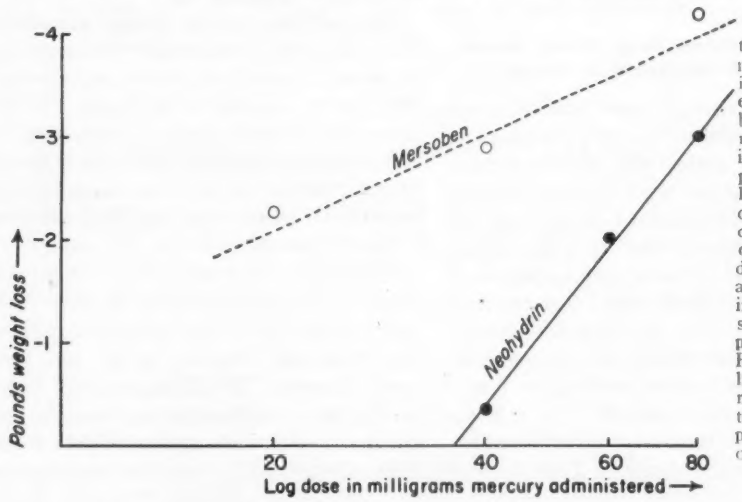

Fig. 2.—When the effects of two mercurial diuretics given in equivalent doses but by different routes of administration are compared, at the lower dose the oral diuretic chlormerodrin. (Neohydrin) is inactive and consequently inferior to Mersoben given parenterally. However, at larger doses the responses to the two drugs approximate each other.

patient's subjective comments were used for evaluation, the number of patients responding to placebo was reduced. When sodium excretion, which is a specific response to this drug, was used for evaluating the response, only 4% responded to placebo whereas 91% responded to chlormerodrin. A similar number (93%) responded to chlormerodrin when evaluated under double-blind conditions. These observations emphasize the importance of specific objective tests for evaluating the response to drugs. Moreover, they dramatize the importance of developing better objective tests for evaluating drugs, particularly in the field of neuropsychiatry, where there is a paucity of

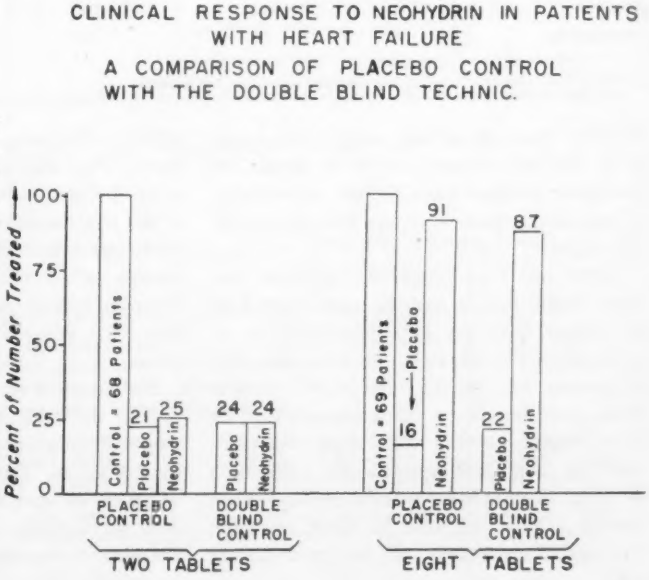

Fig. 3.—Comparison of subthreshold dose of a potent diuretic chlormerodrin (Neohydrin) and a placebo, employing simple placebo replacement and the double-blind technique for evaluating the responses. These same patients were then observed again in a similar way, but the doses of both the placebo and the diuretic were increased fourfold, thus exceeding the diuretic threshold of chlormerodrin.

objective tests and there is so much dependance on subjective information.

Evaluation of Potent Drugs Which Require Strict Individualization of Dosage

In some instances, it is not feasible to use double-blind techniques or even to alternate the drug being studied with placebo because of the necessity for strict vigilance and for the exacting, individualized dosage required. This is particularly true of potent drugs that affect blood pressure, such as ganglionic blocking agents. When these drugs are used, it is necessary that the dose be adjusted carefully for each patient; an example illustrating the dose titration method for pentolinium is seen in Figure 4A. The extreme range of dosage response with some antihypertensive drugs is shown in Table 3. Fortunately, there is usually very little doubt as to the effectiveness of these agents on the blood pressure even though, admittedly, a large psychogenic component is present in this disease.

After effective ganglionic blockade has been established, it may be very hazardous to change from the experimental agent to a placebo. For example, we have observed a number of patients who were changed from pentolinium or from hexamethonium to a placebo or who voluntarily discontinued the drug and subsequently suffered a cerebral hemorrhage within several days due to a rapid increase in blood pressure, frequently in excess of the pretreatment levels. Schroeder [1] has also reported this unfortunate complication.

The effective dosage range of potent drugs may vary considerably from patient to patient, particularly with antihypertensive agents. As shown in Figure 4B, the same dose of mecamylamine administered to two patients produced an excessive response in one, whereas in the other it produced a response much greater than was observed when a placebo was given to the first patient.

The author was a member of a drug panel recently. The results of a double-blind study were reported in which a standard dose of two ganglionic blocking agents had been used. However, the investigator had failed to take into consideration the variations encountered with such agents (Table 3 and Figs. 4A and 4B); thus, his results were invalid. The only conclusion that could be drawn from this study was that the investigator did not have an adequate knowledge of the pharmacodynamics of the drugs used. Experience has shown that it is difficult enough to use these agents even when the clinician knows exactly what he is giving and what serious side-effects can and do occur.

An examination of Table 3 shows immediately the wide range of dosage requirements in a group of patients with severe hypertension. For example, in the group of patients treated with hexamethonium and pentolinium, the daily requirement of the patient requiring the largest dose of the

TABLE 3.—*Dosage Range Required to Produce Blood Pressure Reduction and Intolerable Side-Effects in Patients with Hypertension*

Drug	No. Patients Treated	Smallest Therapeutically Effective Dose Required in Any 1 Patient*	Largest Therapeutically Effective Dose Required in Any 1 Patient*	Average Dose†	Intolerable Side-Effects	
					Minimum Dose*	Maximum Dose*
Hexamethonium	75	63	7,000	2,307	125	9,500
Pentolinium	75	20	2,200	341	40	2,800
Mecamylamine	50	4	210	17	5	200
Reserpine	12	0.2	2.0	1.0	1	60
Protoveratrine	36	0.8	8.0	2.4	—	—

* Total dose in milligrams per 24 hours required to produce this response.
† Average effective dose required to produce optimum effects without intolerable side-effects (milligrams per 24 hours)

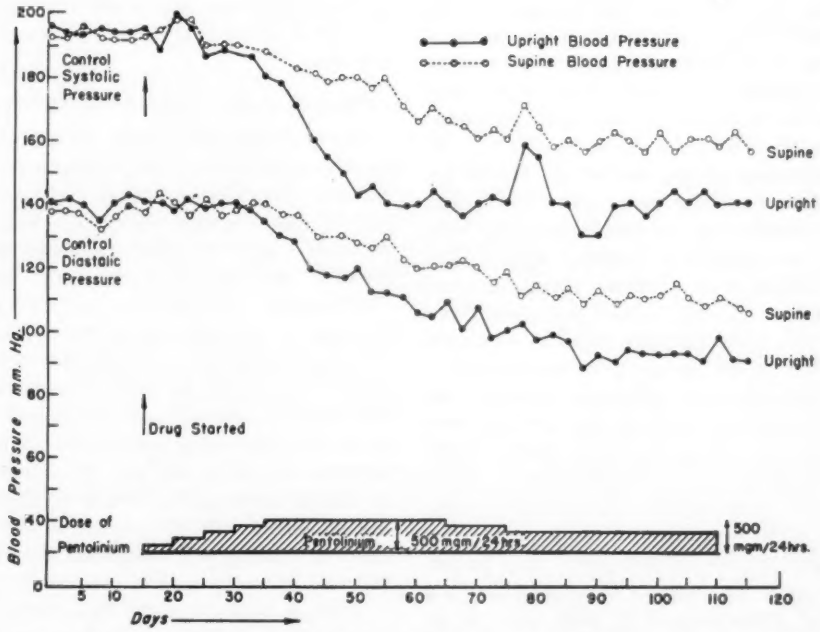

Fig. 4A.—Dose titration of pentolinium. The drug was ineffective in progressively increasing doses until a threshold response was reached at 400 mg. per day. When the dose was increased by another 100 mg., there was a sharp reduction in blood pressure, thus demonstrating the necessity of adequate dosage before an effective response can be obtained.

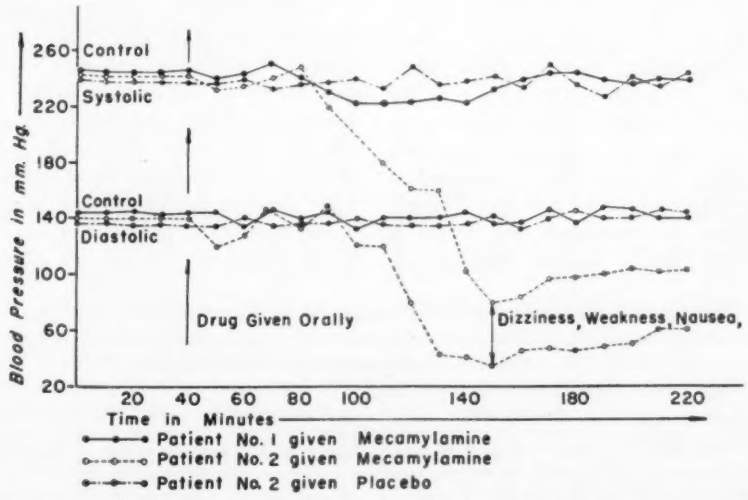

Fig. 4B.—The response of 2 patients with hypertension to the same dose of a ganglionic blocking agent, mecamylamine. Patient No. 1 obtained no reduction in blood pressure when given 10 mg. of the drug. Patient No. 2 likewise obtained no reduction in blood pressure when given a placebo, but when 10 mg. of the drug was given, an excessive reduction in blood pressure followed. This was associated with marked side-reactions, thus emphasizing the necessity for strict individualization of the dose when this drug is used. (Reproduced with permission from Moyer & Associates, A. M. A. Arch. Int. Med. September, 1956.)

drugs was 100 times that required by the patient using the smallest dose, yet the blood pressure response was similar. One might ask whether the small dose requirement was due largely to a psychogenic response. This possibility was ruled out by the administration of placebo for one month before the blocking agent was started and, furthermore, by the substitution of placebo for the ganglionic blocking agent. This was followed by a prompt increase in blood pressure. There is also the observation that the blood pressure response was much greater in the upright position, which is a typical reaction to ganglionic blockade. We can, therefore, conclude that at least some drugs are not applicable to either double-blind studies or placebo-substitution studies because they require a strict individualization of the dose. In fact, using potent drugs in such studies (double-blind) may be hazardous to the patient. There is seldom any doubt concerning effect with these drugs, otherwise the substitution of placebos for the active drug would probably not be contraindicated.

When potent drugs with potentially dangerous side-effects are evaluated, it is best to use the placebo control procedure whenever possible rather than the double-blind technique. This applies particularly to the experienced investigator who maintains an attitude of objectivity. Better insight into specific drug reactions can be obtained if he knows exactly what he is doing. There is no substitute for experience and insight in clinical investigation and an objective investigator, i.e., one who is not striving for the Nobel Prize every time he studies a new drug.

The Use of the Double-Blind Technique

The double-blind technique is basically a method in which the drugs dispensed are under the control of a neutral observer. In such a study, neither the patient nor the therapist knows whether the drug being given is the placebo or the active drug. The purpose is to overcome prejudices on the part of the investigator, thus making the drug evaluation more objective. If the drug is applicable to such an evaluation, double-blind controls can be an effective means of overcoming inexperience, unwarranted enthusiasm, and lack of objectivity in clinical investigation. Table 4, illustrating the results with chlorpromazine (Thorazine) in treating psychoneuroses, illustrates this well.

Table 4 shows that the experienced investigator who evaluates drugs frequently is able to obtain virtually the same results by using either a simple placebo-substitution technique or the double-blind technique. It also shows that a group of interns and residents who had very little interest in clinical investigation and who studied the drug merely as part of their routine hospital duty obtained different results when different techniques were employed. For these investigators, the double-blind technique was a far superior method of drug study, since it minimized false beneficial effects reported by investigators who are not objective in

TABLE 4.—*Clinical Response to Chlorpromazine for the Treatment of Psychoneuroses*

Drug	No. Patients Treated	Therapeutic Improvement in Per Cent of Those Treated								
		No. Controlled			Placebo Control			Double-Blind		
		Poor	Good	Excellent	Poor	Good*	Excellent*	Poor	Good*	Excellent*
Experienced investigator	100	33	20	47	44	20	36	47	23	30
Residents	100	19	24	57	32	21	47	42	21	37
Interns	100	17	22	61	26	18	56	40	22	38

* Includes only those patients who responded to the chlorpromazine but not to placebo. The patients who responded equally as well to placebo are included in the failure group (poor).

their approach. For example, when no placebos were used by the interns, excellent results were observed in 61% of the patients. When placebos were employed, the results were about the same. However, when the intern did not know when he was using the drug and when he was using the placebo (double-blind technique), the excellent results dropped to 38%. The double-blind procedure is particularly useful in the field of neuropsychiatry when subjective response is the primary objective and a wide therapeutic index frequently exists between the effective dose and the dose producing severe side-effects. This technique is particularly useful in the evaluation of drugs used for the treatment of psychoneuroses, since the only method for drawing conclusions concerning the therapeutic efficacy is based on subjective information. In this type of patient we have observed beneficial effects of placebo in as high as 60% of patients so treated. In fact, it frequently becomes impossible to separate the benefits derived from psychotherapy from those derived from drug therapy. For example, who is to say that the patient who has been bedfast for six months is not suffering from concurrent psychoneurotic disturbances that would be alleviated rapidly by curing his organic disease, and vice versa?

When employing double-blind techniques, or even placebo substitution, it is important to avoid using doses considerably in excess of those that are therapeutically effective. If this is done with any frequency, the patients may object because of side-effects and refuse further therapy. Thus, a potentially useful drug would be discarded unjustly on the grounds of patient intolerance simply because effective, well-tolerated dosage ranges had not been established before employing such techniques. Unless these dosage levels are first determined, the investigator is at considerable disadvantage in evaluating the importance, or potential seriousness, of resultant side-reactions.

Table 5 shows the effects of overdosage. Two antiemetic agents, Drugs A and B, were given in doses of 200 mg. A psychogenic reaction was produced against Drug B because the dose was excessive, and two out of three patients refused to take it, saying that "it was no good." When the drug was later disguised and administered in doses of 80 mg. per day, it was equally as effective as Antiemetic A, and side-effects were not significantly different. The only apparent difference between the two drugs was the therapeutic index or range between the effective antiemetic dose and the dose which produced intolerable side-reactions. In fact, Antiemetic Agent B seemed to be slightly superior for prevention of nausea and vomiting when an 80 mg. dose was used.

TABLE 5.—*A Comparison of Two Different Antiemetics*

	Antiemetic A	Antiemetic B
Dose 80 mg./day		
No. patients treated	30	30
Beneficial effect	22	28
Severe side-effect	3	5
Refused further treatment	1	0
Dose 200 mg./day		
No. patients treated	30	30
Beneficial effect	23	25
Severe side-effect	5	26
Refused further treatment	3	20

Finally, one must be cognizant of the possibility of drug tolerance developing in patients who receive continuous medication over prolonged periods of time. However, the loss of drug effect does not mean necessarily that an initial response which was later lost was entirely a psychosomatic response and was not originally a valid response. This must also be kept in mind when a placebo is substituted intermittently for active therapy; it is a good control procedure to use placebos, when feasible, and at intervals, when a course of therapy is being evaluated on a long-range basis. Table 6 shows that the over-all response in a group of psychoneurotic patients treated with chlorpromazine decreased after six months' therapy. Therefore, it appears that

TABLE 6.—*Results with Chlorpromazine in Psychoneuroses Showing Reduction in Response Rate After Six Months of Treatment*

Initial Observations	No.	Therapeutic Results: Excellent		Good		Poor	
		No.	Per Cent	No.	Per Cent	No.	Per Cent
No. placebo	200	115	57.5	51	25.5	34	17
Placebo control	200	101	50.5	44	22	55	27.5
Double-blind control	200	98	49	33	16.5	69	34.5
Observations after 6 mo.*							
No placebo	108	54	50	31	29	23	21
Placebo control	108	43	40	26	24	39	36
Double-blind control	108	40	37	23	21	45	42

* These 108 patients are from the group that initially obtained a good or excellent response to chlorpromazine.

patients who show a good initial response to chlorpromazine tend to become unresponsive after prolonged therapy.

Conclusions

It is logical to conclude that there is no single approach which is applicable to all agents in the therapeutic evaluation of a drug. There is no substitute for adequate clinical pharmacology plus a sound knowledge of the characteristics of the drug under test. When this has been done, then, and only then, can we approach an evaluation of the psychogenic responses unrelated to the specific drug effect as compared to the specific drug response. It is becoming increasingly difficult to separate nonspecific psychosomatic drug responses from specific drug effects in the evaluation of drugs that affect the central nervous system, particularly those used for treating psychiatric conditions. Under these circumstances, specific responses to drugs fade progressively into nonspecific psychological effects. The evaluation of this grey zone presents difficulties, chiefly because of the lack of objective tests for evaluating drugs in mental and emotional disturbances. When the use of subjective criteria is essential, placebo substitution is a requirement for evaluating therapeutic agents. If the range between maximum therapeutic effect and intolerable side-reactions is sufficiently wide, double-blind procedures may be the method of choice for evaluating therapeutic efficacy of drugs used for specific disease entities.

REFERENCE

1. Schroeder, H. A., and Morrow, J. D.: The Control of Arterial Hypertension by Hyphex with an Evaluation of Other Methods of Therapy, M. Clin. North America 37:991 (July) 1953.

Acute Spontaneous Cerebral Vascular Accidents in Young Normotensive Adults

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It is generally conceded that cerebral vascular disease reaches its peak incidence in the later decades of life. Although cerebral embolism and primary subarachnoid hemorrhage are more evenly distributed among the various age groups, cerebral thrombosis and intracerebral hemorrhage occur most frequently in the fifth to eighth decades. In a tabulation of age incidence in 245 necropsied cases of cerebral vascular lesions, Aring and Merritt [1] indicate that 4% of the cases of intracerebral hemorrhage and only 1% of the cases of cerebral thrombosis occurred in persons under the age of 40. It must be remembered that these figures relate to necropsied cases and are probably lower than those which might obtain in a clinical series.

Accordingly, when the apoplectic onset of a neurologic disorder occurs in a normotensive person under the age of 40, the etiologic diagnosis becomes a matter of more than ordinary interest to the neurologist. The widespread use of arteriography with the demonstration of major vascular lesions in some of these patients has rendered a glib diagnosis of multiple sclerosis untenable. Similarly, the recent advances in the serodiagnosis of syphilis and the precipitous decline in incidence of this disease are closing another popular diagnostic haven.

There have been scattered case reports concerned with the etiology of cerebral vascular accidents in young people. Pötzl,[2] in 1934, reported 10 cases in persons under 40 years of age where the etiology was attributed to embolization, nicotine, encephalitis lethargica, and primary subarachnoid hemorrhage. None of his patients were hypertensive. Elkington [3] (1935) was impressed by the occurrence of acute cerebral disturbances in five young adults without previous evidence of cardiovascular disease. The oldest patient in his series was 39. One of these patients was necropsied, and a telangiectasis of the pons and the left middle cerebellar peduncle was discovered. Apparently this finding led the author to hypothesize that hemorrhage into a preexisting vascular anomaly might constitute a likely cause for cerebral vascular accidents involving the pons in the younger age groups.

Dixon [4] (1947), discussing the problem of hemiplegia in young adults, collected 16 cases of "sudden stroke" in patients between the ages of 20 and 40. He was unable to determine the etiology in 11 of these 16 cases and concluded that the phenomenon of "strokes" in young adult life might be the result of either a venous thrombosis in the Rolandic system of veins or a hemorrhage, thrombosis, or embolus in the cerebral arterial system. Krainer [5] (1947) reported seven fatal cases of cerebral thrombosis in young adults. The etiology was attributed to syphilis in one, cerebral malaria in one, mycotic arteritis in three, and intracranial aneurysm in one.

Effron and co-workers [6] (1949) reported two instances of nontraumatic cerebral hemorrhage in adolescence. His first patient was a 13-year-old girl who suffered a large spontaneous intracerebral hemorrhage in-

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volving the right occipital lobe. The second case was that of a 14-year-old boy who apparently had one episode of stiff neck a few months prior to a fatal massive hemorrhage in the area supplied by the left anterior cerebral artery. Although the source of the hemorrhage was not discovered at necropsy, it is possible that an underlying vascular anomaly was obscured by the hemorrhage.

Elvidge[7] (1951) reported six cases of thrombosis of the internal carotid artery and four cases of thrombosis of the middle cerebral branches with arteriographic studies. It is of interest that four of his six patients with carotid thrombosis and two of his four patients with thrombosis of branches of the middle cerebral artery were under the age of 40. These patients were not hypertensive. Fisher[8] (1951), after reviewing the literature on occlusion of the internal carotid artery, made the following statement: "The relatively large number (of these patients) in their teens or twenties has led to the clinical dictum that unexplained hemiplegia in a young person may well mean thrombosis of the internal carotid artery."

In a recent paper on cerebral thrombosis in young adults, Berlin and co-workers[9] emphasize that although one should search for all possible etiologic factors when confronted with the problem of suddenly developing hemiplegia in a young adult, this investigation often proves fruitless. They present 13 cases of acute cerebrovascular lesions in young adults between the ages of 18 and 34 years. Diagnostic procedures failed to uncover evidence of hemorrhage, emboli, hypertension, neoplasm, diabetes, blood dyscrasias, or vascular anomalies. They point out that thrombosis of cerebral arteries attributable to premature vascular degeneration is also a cause of acute neurologic syndromes in young adults. The authors contrast the general reluctance to accept this etiology for the apoplectic development of focal cerebral signs in young people with the recognition accorded premature vascular disease as the etiologic factor in coronary occlusion in the young.

The following selected cases which have been studied at the Vanderbilt University Hospital (VUH) and the Thayer Veterans Administration Hospital (VAH) are presented briefly to illustrate the varied etiology

Summary of Case Material

Case No.	Age at Onset	Blood Pressure	Serology	C.S.F. Protein	Diagnosis
1	30	130/80	Neg.	20	Disseminated lupus erythematosus
2	37	104/68	Neg.	52	Scleroderma
3	27	128/90	Neg.	46	Thromboangiitis obliterans
4	33	94/50	Neg.	79	Thromboangiitis obliterans
5	26	120/60	Neg.	85	Thrombotic thrombocytopenic purpura
6	38	110/60	Neg.	21	Fibrinogenopenia of pregnancy
7	27	135/90	Neg.	26	Postmeasles hemiplegia
8	24	128/44	Neg.	--	Subacute bacterial endocarditis
9	39	124/84	Neg.	--	Angiomatous malformation
10	41	114/84	Neg.	80	Postpartal cerebral venous thrombosis
11	31	110/70	Neg.	17	Spontaneous subcortical hematoma
12	23	120/80	Pos.	52	Meningovascular syphilis
13	33	115/85	Pos.	42	Vascular neurosyphilis
14	29	135/90	Neg.	50	Thrombosis, middle cerebral artery, cause unknown
15	39	140/85	Neg.	34	Thrombosis, middle cerebral artery, cause unknown
16	32	120/80	Neg.	49	Thrombosis, middle cerebral artery, cause unknown
17	32	140/90	Neg.	82	Thrombosis, middle cerebral artery, cause unknown
18	32	130/80	Neg.	38	Thrombosis, middle cerebral artery, cause unknown

of cerebral vascular accidents in young patients. The 18 patients in this study were under 40 years of age, with the exception of case 10, where the patient's age was 41. None of these patients was found to have clinical evidence of hypertensive vascular disease. This case material is summarized in the Table.

Report of Cases

CASE 1.—This 30-year-old Negro man was admitted to the hospital on Oct. 16, 1951, complaining of paralysis of the right extremities. His illness began suddenly four days prior to hospitalization with numbness and weakness of the right upper and lower extremities which progressed to a frank paralysis within a 48-hour period. No loss of consciousness was reported.

During the previous two years he had been admitted to the hospital on 10 occasions for migratory thrombophlebitis of the legs and was treated with anticoagulants and lumbar sympathectomy.

On examination he was found to be moderately aphasic with a right spastic hemiplegia. His blood pressure was 130/80. The cerebrospinal fluid was normal with 1 lymphocyte per cubic millimeter and 20 mg. of protein per 100 ml. The serologic test for syphilis and a sickle-cell preparation were negative. An electrocardiogram was consistent with both anterior and posterior myocardial infarctions. A muscle biopsy was considered compatible with the vasculitis of disseminated lupus erythematosus with other features resembling the changes seen in dermatomyositis.

His convalescence was impeded by the occurrence of a focal convulsion on Oct. 30, 1951. It began in the right hand and became generalized with loss of consciousness. Again the cerebrospinal fluid was normal. He improved and was discharged.

Diagnosis.—Disseminated lupus erythematosus with thrombosis of the middle cerebral artery.

CASE 2.—This 37-year-old white man was admitted to the hospital on Dec. 31, 1952, because he had awakened in the morning with a paralysis of the right arm and leg and difficulty in speaking.

The diagnosis of scleroderma with Raynaud's phenomenon had been established 18 months before, during a previous hospitalization, when a skin biopsy was obtained.

On examination the typical skin changes of scleroderma were apparent. The skin seemed to be taut over the face, hands, and feet. His blood pressure was 104/68. There was a right hemiparesis with a right central facial weakness. He also exhibited a nominal aphasia. The cerebrospinal fluid protein was 52 mg. per 100 ml., and the nonprotein nitrogen was normal. Intravenous corticotropen (ACTH) therapy resulted in no significant benefit.

Diagnosis.—Scleroderma with thrombosis of the left middle cerebral artery.

CASE 3.—This 27-year-old white man became aware of pain in his feet, associated with intense pallor upon exposure to cold, about two years prior to his hospitalization on May 22, 1953. Six months before admission he experienced the sudden onset of speech difficulty, weakness of the right arm and leg, and impairment of vision toward the right side. This gradually cleared, but about four months later he noted the sudden onset of numbness and weakness of the left extremities, which subsequently receded. He learned that the pain in his feet was relieved by placing them in a dependent position. He had been smoking two packages of cigarettes daily for the previous 10 years.

His blood pressure was 128/90. The positive neurologic findings included a mild nominal aphasia, a slight central right facial weakness, and generally hyperactive reflexes. The plantar response was extensor on the left and equivocal on the right.

Serologic tests for syphilis were negative. The cerebrospinal fluid was entirely normal with a protein content of 46 mg. per 100 ml. A muscle biopsy, a pneumoencephalogram, and a left carotid arteriogram were normal. An electroencephalogram was suggestive of a generalized cortical dysfunction of a nonepisodal type. An electrocardiogram was consistent with an old posterior myocardial infarction.

A bilateral lumbar sympathectomy was done. Following this procedure he had several generalized convulsions. He was treated with anticoagulants and discharged after 18 months' hospitalization.

Diagnosis.—Thromboangiitis obliterans with bilateral cerebral thrombosis.

CASE 4.—This 33-year-old white man was admitted to the hospital on Sept. 16, 1950, because of paralysis of the right extremities. He suddenly developed a severe headache 15 days prior to admission, which was followed, within 24 hours, by a right-sided paralysis.

On examination his blood pressure was 94/50. There was a pronounced expressive aphasia and a spastic right hemiplegia with an extensor plantar response on that side. Roentgenograms of the skull were normal. The cerebrospinal fluid protein was 79 mg. per 100 ml., and no cells were seen. An electroencephalogram was normal. He improved and was discharged on Nov. 22, 1950.

He was readmitted on Aug. 30, 1952, complaining of pain in the foot, and had developed a gangrenous area of ulceration between the third and fourth digits of the right foot. At that time a history of heavy smoking was obtained. A right midcalf amputation was necessary. The pathologic

examination of the amputated foot disclosed the vascular lesions of thromboangiitis obliterans. On Jan. 13, 1953, he had a generalized convulsion. This was not followed by any change in his neurologic signs or in the cerebrospinal fluid.

Diagnosis.—Thromboangiitis obliterans.

CASE 5.—This 26-year-old white man was admitted to the hospital on June 17, 1955, because of headache, confusion, transient speech difficulty, jaundice, and weakness of three weeks' duration.

He had enjoyed good health until three weeks prior to admission, when he began to have headaches associated with tingling of the right upper extremity. During the 10 days preceding hospitalization he experienced transient difficulty in speaking on two occasions. Headache became worse and was associated with mental confusion during the few days prior to admission. There was also a history of a few episodes of hematemesis during this illness.

On examination he was a mildly jaundiced and acutely ill young man who appeared confused but was oriented. His blood pressure was 120/60. There were scattered ecchymoses over the thorax and extremities. He exhibited a mild left hemiparesis, and the left plantar response was extensor.

Hematologic examination revealed an icterus index of 15, hemoglobin 7 gm. per 100 ml., RBC 2,400,000, hematocrit 22%, and platelet counts of 7000 and 10,000. The coagulation time was 45 minutes, and the bleeding time was more than 30 minutes.

The cerebrospinal fluid contained 85 mg. per 100 ml. of protein and no cells. The electroencephalogram was considered indicative of a diffuse cortical abnormality. The bone marrow pattern was consistent with that of idiopathic thrombocytopenic purpura plus that of hemolytic anemia. Improvement followed cortisone therapy.

Diagnosis.—Thrombotic thrombocytopenic purpura.

CASE 6.—This 38-year-old white woman was admitted to the hospital in a semicomatose state on May 23, 1953. The day prior to admission she complained of headache and several hours later had a generalized convulsion followed by stupor and a right-sided paralysis. She had been pregnant four and one-half months at the time of this illness.

On examination she appeared pale, and many petechiae were detected over her trunk and extremities. Her blood pressure was 110/60. She responded only to noxious stimuli. There was a right central facial weakness, and the deep reflexes were increased on that side. The right plantar response was equivocal; the left was flexor.

The cerebrospinal fluid pressure was 120 mm., and the fluid was slightly blood tinged at first but cleared rapidly. The cerebrospinal fluid protein was 21 mg. per 100 ml. The bleeding time was more than 1 hour, and the clotting time was 35 minutes. Further laboratory studies revealed evidence of fibrinogen deficiency (plasma fibrinogen 44 mg. per 100 ml.) and thrombocytopenia (platelet count was 35,000 per cubic millimeter of blood).

There was a return of fibrinogen and platelet values to a normal range following several transfusions of whole blood. Further hematologic studies during the remainder of her pregnancy were normal, and the subsequent delivery was not complicated. On neurological examination following delivery the persistent neurologic signs included a spastic right hemiparesis with right homonymous hemianopsia, right hemihypesthesia and minimal dysphasia.

Diagnosis.—Fibrinogenopenia during pregnancy.

CASE 7.—This 27-year-old white woman was admitted to the hospital on June 3, 1940, complaining of paralysis of the left extremities. She had measles 3 weeks prior to admission and about 10 days later noticed a tingling of her left hand. Within the subsequent 48 hours her left arm and leg became paralyzed.

On examination she was found to have a left spastic hemiplegia. Her blood pressure was 135/90. The serologic test for syphilis was negative, and roentgenograms of the skull were normal. The cerebrospinal fluid contained 4 white blood cells per cubic millimeter and a protein content of 26 mg. per 100 ml. Her course was afebrile, and she made a partial recovery during the ensuing year.

Diagnosis.—Postmeasles hemiplegia.

CASE 8.—This 24-year-old white woman was admitted to the hospital on March 30, 1945, in a semicomatose state a few hours following a generalized convulsion. There was a background of rheumatic heart disease. She had been hospitalized elsewhere six months previously because of chills, fever, and dyspnea and improved following the administration of penicillin and digitalis. One week prior to admission she observed small red tender spots on her palms.

On examination there was a right hemiplegia, nuchal rigidity, pallor, clubbed fingers, and cardiac murmurs. Her blood pressure was 128/44. The cerebrospinal fluid was uniformly bloody and under greatly increased pressure.

Her hemiplegia persisted, and she died several months later. At necropsy anaerobic streptococci were cultured from the heart valves. There were multiple bilateral areas of cerebral encephalomalacia, and the right posterior cerebral artery contained an organizing embolus.

Diagnosis.—Subacute bacterial endocarditis with cerebral embolism.

CASE 9.—This 39-year-old white man was admitted to the hospital on Feb. 17, 1954, because of right-sided paralysis. His disability began suddenly 10 days before admission, when he experienced severe headache upon awakening. The headache became worse and was associated with nausea, vomiting, and weakness of the right extremities. There was no loss of consciousness.

On examination he had a right hemiparesis, with increased deep reflexes and an extensor plantar response on that side. The right pupil was larger than the left. The ocular fundi appeared normal. No intracranial bruit was heard. There was considerable nuchal rigidity. The blood pressure was 124/84.

The cerebrospinal fluid was grossly bloody and under increased pressure. An electroencephalogram was indicative of a localized cortical abnormality involving the anterior and posterior temporal regions on the left. A left carotid arteriogram revealed an angiomatous configuration of the posterior branches of the left middle cerebral artery.

Diagnosis.—Angiomatous malformation of the middle cerebral artery, with subarachnoid and intracerebral hemorrhage.

CASE 10.—This 41-year-old white woman was admitted to the hospital on Jan. 22, 1948, and was delivered of her second child without incident. Two days following delivery she began to complain of intermittent frontal headache and paresthesias of the right extremities. There was also transient speech difficulty. On the eighth postpartum day she had a focal convulsion which began in the right hand and became generalized. Postictally there was a right hemiplegia, with a right central type of facial weakness and astereognosis of the right hand. The eyegrounds were normal, and her blood pressure was 114/84.

The cerebrospinal fluid pressure was 100 mm.; there were 3 white blood cells per cubic millimeter and a protein content of 80 mg. per 100 ml. Three more focal seizures followed during the subsequent 24 hours. During the ensuing two weeks she was treated with anticonvulsants and anticoagulants. The hemiparesis cleared almost completely during this brief interval. She remained entirely asymptomatic during the subsequent seven years.

Diagnosis.—Postpartal cerebral venous thrombosis.

CASE 11.—This 31-year-old white man was admitted to the hospital on June 23, 1948, two days following the onset of focal seizures beginning in the right hand.

On examination he had a right spastic hemiplegia, with an expressive aphasia and a right hemihypesthesia. The blood pressure was 110/70.

The cerebrospinal fluid was under a pressure of 200 mm. (patient tense) and contained 5 white blood cells per cubic millimeter. The protein content of this fluid was 17 mg. per 100 ml. Serologic tests for syphilis were negative, and there was no history of trauma.

A ventriculogram was normal, but in view of the focal character of his seizures a left frontoparietal craniotomy was done. Beneath the discolored cortex of the superior parietal lobule was found a subcortical hematoma. Subsequently he continued to have seizures and a right hemiparesis. A left carotid arteriogram in 1950 was normal.

Diagnosis.—Spontaneous subcortical hematoma.

CASE 12.—This 23-year-old Negro man was admitted to the hospital Sept. 15, 1938, with a three-week history of right-sided convulsions and progressive right hemiparesis. Four months prior to the present illness he had a painless penile lesion.

On examination there was a right spastic hemiparesis with an extensor plantar response on that side. There was no aphasia or nuchal rigidity. The blood pressure was 120/80.

The cerebrospinal fluid contained 302 lymphocytes per cubic millimeter and a protein content of 52 mg. per 100 ml. The blood and cerebrospinal fluid serologic tests for syphilis were positive. He improved following treatment with arsenicals and bismuth.

Diagnosis.—Meningovascular syphilis.

CASE 13.—This 33-year-old white man was admitted to the hospital on Jan. 13, 1944, because of the sudden onset of paralysis of the left extremities three days previously. Six years before he had a penile lesion and a positive serologic test for syphilis. He was treated with arsenicals and bismuth during a two-year period.

On examination there was a spastic left hemiparesis and a left hemihypesthesia. The blood pressure was 115/85. The Kahn and Wassermann tests were positive in the blood. The cerebrospinal fluid contained 1 white blood cell per cubic millimeter and 42 mg. of protein per 100 ml. The cerebrospinal fluid Wassermann was negative.

Diagnosis.—Vascular neurosyphilis.

CASE 14.—This 29-year-old white woman was admitted to the hospital on June 16, 1941, complaining of paralysis. Three weeks prior to admission she noted, shortly after awakening, the rapid onset of progressive numbness and weakness of her left extremities.

On examination there was noted a spastic left hemiplegia and a mild left hemihypesthesia. There was astereognosis of the left hand. The blood pressure was 135/90, and the serologic test for syphilis was negative. Roentgenograms of the skull were normal. The cerebrospinal fluid contained 3 white blood cells per cubic millimeter and a protein content of 50 mg. per 100 ml.

Diagnosis.—Thrombosis, partial, middle cerebral artery, due to unknown cause.

CASE 15.—This 39-year-old white man was admitted to the hospital on June 17, 1955. He had experienced the abrupt onset of a right hemiplegia and aphasia six months before hospitalization. There was no history of headache, vomiting, or stiff neck.

On examination there was found only a mild spastic right hemiparesis. The blood pressure was 140/85, and the serologic test was negative. The cerebrospinal fluid contained 1 white blood cell per cubic millimeter and 34 mg. of protein per 100 ml. Roentgenograms of the skull and an electroencephalogram were normal.

Diagnosis.—Thrombosis, middle cerebral artery, due to unknown cause.

CASE 16.—This 32-year-old Negro man was admitted to the hospital on May 10, 1955. Two days before admission he suddenly noted paralysis of the right extremities and speech difficulty.

On examination he was obviously aphasic and had a right hemiparesis with extinction phenomena on that side. No intracranial bruit was heard. His blood pressure was 120/80. The cerebrospinal fluid protein was 49 mg. per 100 ml., and no cells were present in the fluid. The blood and cerebrospinal fluid serologic tests were negative. One of the branches of the left middle cerebral artery was found to be occluded on arteriography.

Diagnosis.—Thrombosis, partial, middle cerebral artery, due to unknown cause.

CASE 17.—This 32-year-old white man was admitted to the hospital on May 17, 1953. He experienced a momentary lapse of consciousness six days before admission, followed by headache. Several hours later he awakened with nausea and vomiting and a few hours thereafter noted paralysis of his left extremities. He improved progressively during the next few days.

On examination he was found to have a left hemiparesis involving the upper extremity more than the lower. There was no sensory loss. Visual fields were full to confrontation. Blood pressure was 140/90.

Cerebrospinal fluid examination was remarkable only with respect to the protein elevation of 82 mg. per 100 ml. A pneumoencephalogram, right carotid arteriogram, and electroencephalogram were normal.

Diagnosis.—Thrombosis, partial, middle cerebral artery, due to unknown cause.

CASE 18.—This 32-year-old man was admitted to the hospital on Feb. 18, 1953. He enjoyed good health until four and one-half months before hospitalization, when he experienced the acute onset of numbness and weakness of the right extremities. During the subsequent months he improved gradually, although weakness of the right hand and foot persisted.

On examination there were increased deep reflexes and an abnormal plantar response on the right. A mild right central facial weakness was noted. The visual fields and eyegrounds were normal. Blood pressure was 130/80.

Serologic tests of the blood and cerebrospinal fluid were negative. The cerebrospinal fluid contained 1 white blood cell per cubic millimeter and 38 mg. of protein per 100 ml. Skull roentgenograms and a left carotid arteriogram were normal.

Diagnosis.—Thrombosis, partial, left middle cerebral artery, due to undetermined cause.

Comment

I. Diffuse Arteritis (Cases 1-4)

Disseminated lupus erythematosus, polyarteritis nodosa, dermatomyositis, and scleroderma have certain histopathologic features in common, and these disorders are often referred to collectively as "collagen diseases."

Fundamentally, the pathologic process in this group of diseases involves the collagenous intercellular material, which swells and exhibits a fibrinoid change. The affected areas are infiltrated by polymorphonuclear leucocytes and round cells. Eosinophiles may be present. The fixed connective tissue cells, such as fibroblasts and histiocytes, show variable activity. When these changes involve the media, adventitia, and perivascular tissues, the typical vascular lesions are seen. Kampmeier [10] has suggested that the intensity and the location of the collagen disease reaction determines the particular expression of illness, polyarteritis representing one extreme and scleroderma, the other.

Although the patient in Case 1 had been hospitalized on several previous occasions because of a migratory polyphlebitis, it was his neurologic illness which led to a complete study and recognition of the underlying disease.

As Sedgewick and Von Hagen [11] have emphasized, no consistent neurologic syndrome has yet been defined for either lupus erythematosus or polyarteritis nodosa because of the variable and widespread pathologic changes. However, they noted that lupus erythematosus manifests itself neurologically chiefly by central nervous system syndromes, while polyarteritis nodosa fre-

quently affects peripheral and cranial nerves. Glaser [12] has recently summarized the pertinent literature and the neuropathologic changes in lupus erythematosus. He includes among the neurologic symptoms reported to have occurred during the course of this illness, focal and generalized seizures, transient cranial nerve palsies, hemiparesis, and aphasia. Vascular thromboses were reported in several of the 17 necropsied cases which Malamud and Saver [13] reviewed. In Case 1, as in the three described by Siekert and Clark,[14] evidence of neurologic dysfunction appeared prior to the establishment of the diagnosis of systemic lupus erythematosus.

The close relationship between scleroderma and lupus erythematosus has been mentioned many times in the literature. Klemperer and co-workers [15] pointed out that the fibrinoid degeneration of lupus erythematosus and the collagen sclerosis of scleroderma are morphologic expressions of different phases of a disturbed colloidal collagen system. In a case of scleroderma, Pagel and co-workers [16] found histologic changes indistinguishable from those of disseminated lupus erythematosus and polyarteritis nodosa. In Case 2 of Glaser's series, the clinical picture resembled that of Raynaud's syndrome and suggested a sclerodermatous basis, although the vascular lesions were typical of lupus erythematosus. It is suggested that Case 2 of this series had a similar vasculitis which set the stage for the cerebral thrombosis. In an excellent review of scleroderma, Beigelman and coworkers [17] proposed the term "progressive systemic sclerosis" as reflecting more accurately the diffuse nature of the disease.

Our two cases of cerebral Buerger's disease represent another type of arteritis, although here, too, there are certain features which parallel those seen in the collagen diseases. In their review of this subject, Hausner and Allen [18] found 11 cases of cerebral involvement in a group of 500 patients with thromboangiitis obliterans. The commonest cerebral symptoms which they encountered were transient hemianopia and transitory, constant, or recurrent hemiplegia. In three of their cases, as in our Case 4, the cerebral lesion preceded the symptoms of peripheral vascular disease. Davis and Perret [19] reported 11 cases of cerebral thromboangiitis obliterans, nine of these verified at craniotomy. These patients often present a neurologic syndrome which is remarkably similar to that caused by an intracranial neoplasm.

II. Hematologic Disorders (Cases 5 and 6)

There are a large number of blood dyscrasias which may be responsible for cerebral hemorrhage and thrombosis. The hemorrhagic diseases, including the purpuras, hemophilia, fibrinogenopenia, and hypoprothrombinemia, may be complicated by bleeding within the brain. As Chalgren [20] has stated in his review of this subject, there may be focal neurologic phenomena, such as hemiplegia, aphasia, and visual field defects, subarachnoid hemorrhage, or convulsions, either generalized or focal. The brain hemorrhage which occurs in cases of malignant lymphoma is usually attributed to thrombocytopenia. Sparling and coworkers,[21] discussing involvement of the nervous system by malignant lymphoma, also mention damage to a cerebral vessel by leukemic infiltration of its wall as a possible mechanism to explain cerebral hemorrhage in these diseases.

Sickle-cell disease and polycythemia vera are examples of hematologic disorders in which thrombosis of vessels commonly occurs. Johnson and Chalgren [22] found that hemiplegia constitutes one of the commonest focal neurologic disturbances in polycythemia vera. It is usually the result of vascular thrombosis. In a recent case report, Green [23] described the occurrence of an acute right hemiplegia in a 17-year-old girl with infectious mononucleosis. He suggests that the heterophile antibody titer be determined when investigating the etiology of a cerebral vascular disturbance in a young adult.

Case 5, an instance of thrombotic thrombocytopenic purpura, might well have been

considered in the preceding section because it is closely related to the collagen diseases. Further evidence in this regard has been presented by Laszlo and co-workers,[24] who reported a case which illustrated the association of thrombotic thrombocytopenic purpura and disseminated lupus erythematosus. Platelet thrombi were found at necropsy, and a positive "L.E. cell" preparation had been noted during life. Thrombotic thrombocytopenic purpura is characterized by the triad of hemolytic anemia, thrombocytopenic purpura, and a variable neurologic syndrome due to occlusion of small arterioles. The relevant literature has been well summarized by Ladwig,[25] who also discussed the pathology of the syndrome and its relationship to the collagen diseases. Paralysis was noted in 7 of the 14 cases reviewed by Adams and co-workers.[26]

Case 6, fibrinogenopenia during pregnancy, represents a unique example of presumed intracranial hemorrhage as a part of this uncommon syndrome. Jackson and co-workers[27] reported 10 cases of this hemorrhagic diathesis complicating pregnancy. These authors stated that the most likely mechanism for the production of the fibrinogen deficiency in these cases is the entrance into the maternal circulation of thromboplastic agents from the uterine contents, with resultant intravascular defibrination.

III. Postinfectious Cerebral Vascular Accidents (Case 7)

In most of the cases of cerebral vascular accidents following such acute infections as pertussis, measles, dysentery, influenza, typhoid, pneumonia, diphtheria, typhus, and others, there is usually clinical and pathologic evidence of only one vascular lesion. Ford[28] is of the opinion that there is no resemblance to a hemorrhagic encephalitis. He cites Rolleston's summary of the literature regarding hemiplegia following diphtheria. Of 21 such cases which were necropsied, there was embolism in 13, thrombosis in 3, hemorrhage in 1, and abscess in another. Ford also mentioned the work of Wiesel, who studied the arteries of 300 young subjects who died of various acute infectious diseases and found destructive changes in smooth muscle and the elastic tissue of the media which sometimes resulted in necrosis.

The onset of hemiplegia, as in Case 7, is usually during convalescence and may occur several weeks after the height of the original illness, thereby differing from the hemorrhagic encephalopathy which usually appears during the acute stages of the disease. The normal cerebrospinal fluid and the residual neurologic damage described in Case 7 of this series are characteristic of this entity. In discussing the hemiplegia which may follow pneumonia, Baker and Noran[29] express the viewpoint that the neurologic findings are attributable to an encephalitis, although they agree with Ford's description of the clinical picture, including the normal cerebrospinal fluid findings.

IV. Cerebral Embolism and Subacute Bacterial Endocarditis (Case 8)

Although Case 8 serves as an example of cerebral embolism occurring in a young adult with bacterial endocarditis, this patient with obvious cardiac involvement and a characteristic clinical history did not constitute a diagnostic problem. The subarachnoid hemorrhage must be attributed to hemorrhagic infarction of the brain, since there was no evidence at necropsy of a ruptured mycotic aneurysm.

Krinsky and Merritt[30] found in their study of 100 proved cases of subacute bacterial endocarditis that 31% of the patients showed one or more neurologic manifestations on admission. In 20% the symptoms and signs were so predominantly neurologic that the primary lesion was thought to be in the central nervous system. They emphasized the importance of considering subacute bacterial endocarditis as a diagnostic possibility when a young adult is admitted to a hospital with hemiplegia of sudden onset. Cerebral embolism may also occur in patients with rheumatic heart disease uncomplicated by bacterial endocarditis.

Thrombosis within a dilated or fibrillating auricle or myocardial infarction with detachment of a mural thrombus may be the underlying condition. Cerebral embolization may occur in cases of disseminated lupus erythematosus in which the atypical verrucous endocarditis of Libman-Sacks is present. A consideration of fat embolism is not necessary here, since we are not concerned with traumatic conditions, although Silverstein,[31] in his review of cerebral fat embolism, proposes the hypothesis that alteration in the blood chemistry itself may be the source of fat globules and suggests alkali poisoning and sickle-cell disease as illustrative nontraumatic conditions.

V. Vascular Anomalies (Case 9)

With the increasing use of intracranial angiography during the past decade, the role of saccular aneurysms and angiomatous malformations in the production of apoplectic neurologic syndromes has been well delineated. Case 9, an angiomatous malformation, is employed to illustrate this group.

Cerebral vascular accidents attributable to these vascular anomalies are often seen in patients under 40 years of age. Williams and co-workers,[32] after reviewing 143 necropsied cases of congenital cerebral anrusysms, note that the distribution of these cases increases in number progressively from the second to the sixth decade. These conditions are so frequently the subject of reports in the contemporary neurologic literature that there is little reason to discuss them further.

VI. Postpartal Cerebral Venous Thrombosis (Case 10)

Although the subject of Case 10 is the only patient in this series over the age of 40, most of these postpartum cases have been reported in younger women. The eight cases of "puerperal hemiplegia" reported by Stevens [33] range in age from 22 to 39. This syndrome is characterized by the sudden onset of headache, convulsions, coma, and hemiplegia, appearing several hours to weeks following delivery in a previously healthy patient. Many reports regarding this disorder have appeared in the British literature during the past 15 years (Symonds,[34] Martin and Sheehan,[35] Martin,[36] and Kendall [37]). Gowers,[38] as might be expected, was among the first to recognize cerebral venous thrombosis occurring in the puerperal state. The clinical picture varies with the extent of the thrombosis. It seems likely that only the Rolandic veins were involved in Case 10 of our series. When the thrombosis involves the sagittal sinus, bilateral neurologic signs and increased intracranial pressure are often present.

The etiology of cerebral venous thrombosis during the puerperium remains speculative. The role of anticoagulant therapy is difficult to assess, and although it was employed in our patient, the risk of provoking uterine bleeding when it is given early in the puerperium must be considered. Hemorrhage in the infarcted cerebral areas might also occur as a complication of anticoagulant treatment. Stevens' eight cases all recovered without such measures. The prognosis with regard to life and function is much better in these cases than it is in cerebral artery thrombosis.

VII. Spontaneous Subcortical Hematoma (Case 11)

Although the etiology and pathogenesis of this condition remain obscure, this entity has received increasing attention in the neurosurgical literature of the past two decades. Arterial anomalies, vasospasm, and venous bleeding have been mentioned as possible etiologic factors. No relationship to trauma has been noted. One of the most recent studies is that of Werner,[39] who reported eight cases.

Spontaneous subcortical hematoma occurs in young patients, frequently under the age of 40, as indicated by the reports of Craig and Adson [40] and Klemme.[41] Only one of Werner's eight patients was hypertensive, and hypertension has not been considered etiologically significant in other reports. The clinical picture is characterized by an apoplectic onset with severe headache, often

accompanied by vomiting, and frequently followed by focal or generalized seizures and hemiparesis or hemiplegia. Despite surgical evacuation of the hematoma there is usually permanent residual impairment of function, and there may also be persistent seizures, as demonstrated by Case 11.

VIII. Vascular Neurosyphilis (Cases 12 and 13)

Stokes and co-workers,[42] in their text, "Modern Clinical Syphilology," discuss the differential diagnosis of vascular neurosyphilis, describing the patient with this disorder as one who is "too young for arteriosclerosis," and add that a history of syphilis and a positive serologic test may or may not be present. It is also stated that, "the diagnosis may have to be made by exclusion." Alpers [43] points out that this form of syphilis may be associated with a negative Wassermann reaction of both blood and spinal fluid. In 1937, Howell [44] made the following statement: "In a young adult hemiplegia of sudden onset is more often due to syphilitic thrombosis than to anything else, provided you can exclude embolus, tumor of the brain, and disseminated sclerosis."

On the other hand, Merritt [45] (1955) states that, "A history of a previous syphilitic infection or a positive serologic test for syphilis in the blood or even in the cerebrospinal fluid indicates only the presence of syphilis and does not indicate whether syphilis or arteriosclerosis is the etiologic factor."

Without belaboring the issue it is clear that a precipitous decline in the incidence of syphilis following the introduction of penicillin therapy has resulted in a departure from the viewpoint of Howell, which reflected a majority opinion during the prepenicillin era. It is likely that many incorrect diagnoses of vascular syphilis have been made in the past in young adults with cerebral vascular accidents, particularly when the blood test for syphilis was falsely positive. For it is only during the past several years that the phenomenon of biologic false positivity has been elucidated by means of the Treponema immobilization test. Nelson and Mayer,[46] in 1949, cited by Moore,[47] in 1953, demonstrated a Treponema-immobilizing antibody in the serum of animals and man infected with syphilis or other treponematoses, but not in that of normal persons or of those with nontreponemal diseases. This discovery has greatly simplified the identification of the biologic false-positive reactor.

It seems reasonable to suspect that in former years a young adult with an apoplectic neurologic syndrome and a biologic false-positive serologic test for syphilis would almost certainly have been diagnosed as an instance of vascular neurosyphilis, even in the absence of a previous history of syphilis. The posibility of such an error becomes especially likely when one considers further that such diseases as infectious mononucleosis, malaria, disseminated lupus erythematosus, viral pneumonia, multiple myeloma, sarcoid, and others which may be associated with cerebral vascular accidents in young adults are the very disorders which often lead to a biologic false-positive serologic test. It is probable that this reaction is related to a qualitative or quantitative alteration in γ-globulin.

As Kampmeier [48] has stated, "Since the treatment of syphilis should mean the treatment of a disease and not the treatment of a blood test, careful study is required in the absence of overt manifestations of syphilis." This quotation is particularly appropriate when the papers of Zellermayer,[49] Moore and Mohr,[50] and Stokes and James [51] are reviewed. These workers all agree that the proportion of biologic false-positive reactions in a survey may be as high as 40% to 45% of all positive tests. It is recommended that every positive blood test be repeated, since serologic discord is often a warning of nonspecific positiveness. A very low titer of antibody may also point to a biologic false-positive test. One should also search for a history of a known precipitating cause of the biologic false-positive phenomenon, especially in a per-

son known previously to be seronegative. The simplicity of the penicillin treatment should not tempt the physician to arrive prematurely at a decision regarding the diagnosis of syphilis.

In view of all these considerations it is suggested that, at the present time, syphilitic endarteritis plays a minor etiologic role with regard to cerebral vascular accidents. Cases 12 and 13 have been cited from the records of previous decades out of deference to tradition. One is tempted to question the validity of the diagnosis in Case 13, since a six-year interval and a history of adequate treatment followed the primary stage of the disease.

IX. Other Disorders Associated with Cerebral Vascular Accidents in Young Adults

There are a variety of diseases and toxins which have been etiologically related to apoplectiform neurologic syndromes in young patients. Malaria, carbon monoxide poisoning, and ergotism may be added to the ones previously discussed. Thrombosis of a cerebral artery occasionally follows external compression of a vessel by neoplasm. Murphy [52] reported the case of a normotensive 36-year-old woman with migraine who suddenly developed a right hemiplegia. Detailed laboratory studies, arteriography, and craniotomy were done. The author attributed the cerebral infarction in this case to persistent intracranial arteriospasm. He referred to previous reports of permanent neurologic crippling as residuals of migraine attacks.

X. Cerebral Thrombosis of Unknown Cause (Cases 14-18)

After one has investigated assiduously the various etiologic possibilities in studying an acute cerebral vascular accident in a young adult, it is more than likely that the final diagnosis will be "cerebral thrombosis of unknown cause." It is probable that many of these cases are really attributable to thrombosis of the internal carotid artery, although they are usually classified as thrombosis of the middle cerebral artery, as we have done in this study. The arteriographic studies of the past decade have demonstrated that the traditional diagnostic criteria of ipsilateral blindness and contralateral hemiplegia are often lacking in cases of thrombosis of the carotid system.

Ameli and Ashby [53] reviewed 33 cases of thrombosis of the internal carotid or common carotid arteries and found that 7 of these patients were below the age of 40. They pointed out that although Moniz cited syphilis as the most important etiologic factor in carotid thrombosis, he mentioned only one patient with a history of syphilis, and the Wassermann reaction in that case was negative. None of the six patients presented by these authors had a positive serologic test. In this regard, Elvidge [7] referred to a patient of Krayenbühl and Weber who was considered to have a thrombosis of the internal carotid artery due to syphilis, but on histologic examination of the vessel there was a nonsyphilitic angiitis.

In 14 of the 17 cases of spontaneous thrombosis of the carotid arteries reported by Shapiro and Peyton,[54] no etiology for the thrombosis could be found. Of the three remaining cases, polyarteritis was found in other organs at necropsy in one case, another had polycythemia, and, in the third case, thrombosis developed during convalescence from pneumonia. Two patients in their series were less than 40 years old. Hypertension was present in 3 of the 17 cases.

In speculating about the etiology of the last five cases in our series, we are influenced by the reports in the literature of degenerative vascular changes in young normotensive persons. Keele [55] found that the degree of atheromatous

change in the carotid sinus was related to age rather than to hypertension. Of 55 cases in which histologic studies were done, 6 persons under the age of 40 were found to have atheromatous changes in the carotid sinus. Dörfler [56] studied the internal carotid artery from its entry into the skull until its passage through the dura in 120 cadavers. Microscopic evidence of arteriosclerotic changes was found in 27 people under the age of 40.

In a 4-year-old boy with acute hemiplegia of obscure etiology, Ford [28] found, at necropsy, thrombosis of the middle cerebral artery. There were intimal plaques on the cerebral arteries of this child as well as numerous areas of medial necrosis and degenerative changes in the elastic lamellae.

On the basis of the clinical and pathologic reports in the literature, we are led to conclude that premature arteriosclerotic vascular changes constitute the most important pathogenetic factor in the etiology of spontaneous cerebral vascular accidents in young adults.

Summary

Eighteen selected cases of acute spontaneous cerebral vascular accidents in young normotensive adults are presented.

The diagnoses and subjects for discussion include disseminated lupus erythematosus, scleroderma, thromboangiitis obliterans, thrombotic thrombocytopenic purpura, fibrinogenopenia of pregnancy, postmeasles hemiplegia, subacute bacterial endocarditis, angiomatous malformation, postpartal cerebral venous thrombosis, spontaneous subcortical hematoma, and syphilis, as well as cerebral thrombosis of unknown cause.

It is suggested that the precipitous decline in incidence of all forms of syphilis during the penicillin era has minimized the etiologic importance of syphilis with regard to cerebral vascular accidents in the younger age groups. The phenomenon of biologic false-positive serologic tests is discussed as a probable cause of a mistaken diagnosis of vascular syphilis.

The frequency of thrombosis of the carotid arteries in young normotensive adults is emphasized.

It is concluded that premature arteriosclerotic vascular changes constitute the most important pathogenetic factor in the etiology of spontaneous cerebral vascular accidents in young normotensive adults.

REFERENCES

1. Aring, C. D., and Merritt, H. H.: Differential Diagnosis Between Cerebral Hemorrhage and Cerebral Thrombosis: Clinical and Pathologic Study of 245 Cases, Arch. Int. Med. 56:435, 1935.

2. Pötzl, O.: Über die Zunahme der Apoplexien bei Jugendlichen, Wien. klin. Wchnschr. 47:609, 1934.

3. Elkington, J. St. C.: Cerebral Vascular Accidents Unassociated with Cardiovascular Disease, Lancet 1:6, 1935.

4. Dixon, G. J.: Hemiplegia in Young Adults, Brit. M. J. 2:53, 1947.

5. Krainer, L.: Cerebral Thrombosis in Young Adults, Lancet 1:738, 1947.

6. Effron, B.; Rosenberg, A. A., and Muller, H.: Cerebral Hemorrhage (Nontraumatic) in Adolescence, New York J. Med. 49:1450, 1949.

7. Elvidge, A. R., and Werner, A.: Hemiplegia and Thrombosis of the Internal Carotid System, A.M.A. Arch. Neurol. & Psychiat. 66: 752, 1951.

8. Fisher, M.: Occlusion of the Internal Carotid Artery, A.M.A. Arch. Neurol. & Psychiat. 65:346, 1951.

9. Berlin, L.; Tumarkin, B., and Martin, H. L.: Cerebral Thrombosis in Young Adults, New England J. Med. 252:162, 1955.

10. Kampmeier, R. H.: Vascular Diseases Due to Hypersensitivity: So-Called Diffuse Collagen Disease, Am. Pract. & Digest. Treat. 1:113, 1950.

11. Sedgwick, R. P., and Von Hagen, K. O.: The Neurological Manifestations of Lupus Erythematosus and Periarteritis Nodosa: Report of 10 Cases, Bull. Los Angeles Neurol. Soc. 13:129, 1948.

12. Glaser, G. H.: Lesions of the Central Nervous System in Disseminated Lupus Erythematosus, A.M.A. Arch. Neurol. & Psychiat. 67:745, 1952.

13. Malamud, N., and Saver, G.: Neuropathologic findings in Disseminated Lupus Erythematosus, A.M.A. Arch. Neurol. & Psychiat. 71:723, 1954.

14. Siekert, R. G., and Clark, E. C.: Neurologic

Signs and Symptoms as Early Manifestations of Systemic Lupus Erythematosus, Neurology 5:84, 1955.

15. Klemperer, P.; Pollack, A. D., and Baehr, G.: Diffuse Collagen Disease: Acute Disseminated Lupus Erythematosus and Diffuse Scleroderma, J.A.M.A. 119:331, 1942.

16. Pagel, W.; Woolf, A. L., and Asher, R.: Histological Observations on Dermatomyositis, J. Path. & Bact. 61:403, 1949.

17. Beigelman, P. M.; Goldner, F., Jr., and Bayles, T. B.: Progressive Systemic Sclerosis (Scleroderma), New England J. Med. 249:45, 1953.

18. Hausner, E., and Allen, E. V.: Cerebrovascular Complications in Thromboangiitis Obliterans, Ann. Int. Med. 12:845, 1938.

19. Davis, L., and Perret, G.: Cerebral Thromboangiitis Obliterans, Brit. J. Surg. 34:307, 1947.

20. Chalgren, W. S.: Neurologic Complications of the Hemorrhagic Diseases, Neurology 3:126, 1953.

21. Sparling, H. J., Jr.; Adams, R. D., and Parker, F., Jr.: Involvement of the Nervous System by Malignant Lymphoma, Medicine 26: 285, 1947.

22. Johnson, D. R., and Chalgren, W. S.: Polycythemia Vera and the Nervous System, Neurology 1:53, 1951.

23. Green, I.: Acute Hemiplegia in Infectious Mononucleosis, Neurology 5:366, 1955.

24. Laszlo, M. H.; Alvarez, A., and Feldman, F.: The Association of Thrombotic Thrombocytopenic Purpura and Disseminated Lupus Erythematosus: Report of a Case, Ann. Int. Med. 42: 1308, 1955.

25. Ladwig, H. A.: The Central Nervous System in Thrombotic Thrombocytopenic Purpura, Neurology 3:267, 1953.

26. Adams, R. D.; Cammermeyer, J., and Fitzgerald, P. J.: The Neuropathological Aspects of Thrombocytic Acroangiothrombosis: Clinico-Anatomical Study of Generalized Platelet Thrombosis, J. Neurol. Neurosurg. & Psychiat. 11:27, 1948.

27. Jackson, D. P.; Hartmann, R. C., and Busby, T.: Fibrinogenopenia Complicating Pregnancy, Obst. & Gynec. 5:223, 1955.

28. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, Ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1945, pp. 735-736; pp. 737-738.

29. Baker, A. B., and Noran, H. H.: Changes in the Central Nervous System Associated with Encephalitis Complicating Pneumonia: I. A Clinical Study, Arch. Int. Med. 76:146, 1945.

30. Krinsky, C. M., and Merritt, H. H.: Neurologic Manifestations of Subacute Bacterial Endocarditis, New England J. Med. 218:563, 1938.

31. Silverstein, A.: Significance of Cerebral Fat Embolism, Neurology 2:292, 1952.

32. Williams, R. R.; Bahn, R. C., and Sayre, G. P.: Congenital Cerebral Aneurysms, Proc. Staff Meet. Mayo Clin. 30:161, 1955.

33. Stevens, H.: Puerperal Hemiplegia, Neurology 4:723, 1954.

34. Symonds, C. P.: Cerebral Thrombophlebitis, Brit. M. J. 2:348, 1940.

35. Martin, J. P., and Sheehan, H. L.: Primary Thrombosis of Cerebral Veins (Following Childbirth), Brit. M. J. 1:349, 1941.

36. Martin, J. P.: Venous Thrombosis in the Central Nervous System, Proc. Roy: Soc. Med. 37:383, 1944.

37. Kendall, D.: Thrombosis of Intracranial Veins, Brain 71:386, 1948.

38. Gowers, W. R.: A Manual of Diseases of the Nervous System, Ed. 2, Philadelphia, P. Blakiston's Sons & Co., 1898, Vol. 2, p. 450.

39. Werner, A.: A Study of 8 Surgically Treated Cases of Spontaneous Sub-Cortical Hematoma, J. Neurol. Neurosurg. & Psychiat. 17:57, 1954.

40. Craig, W. McK., and Adson, A. W.: Spontaneous Intracerebral Hemorrhage: Etiology and Surgical Treatment, with a Report of 9 Cases, Arch. Neurol. & Psychiat. 35:701, 1936.

41. Klemme, R. M.: Nontraumatic Intracerebral Hemorrhage with Clot Formation, Surgery 10:434, 1941.

42. Stokes, J. H.; Beerman, H., and Ingraham, N. R.: Modern Clinical Syphilology, Ed. 3, Philadelphia, W. B. Saunders Company, 1944, p. 996.

43. Alpers, B. J.: Clinical Neurology, Ed. 3, Philadelphia, F. A. Davis Company, 1954, p. 427.

44. Howell, C. M. H.: Cerebral Vascular Accidents, Brit. M. J. 1:255, 1937.

45. Merritt, H. H.: A Textbook of Neurology, Philadelphia, Lea & Febiger, 1955, p. 116.

46. Nelson, R. A., Jr., and Mayer, M. M.: Immobilization of Treponema Pallidum in Vitro by Antibody Produced in Syphilitic Infection, J. Exper. Med. 89:369, 1949.

47. The Changing Pattern of Syphilis 1941-1953, Editorial, Ann. Int. Med. 39:644, 1953.

48. Kampmeier, R. H.: Interpretation of the Serologic Test for Syphilis, New Orleans M. & S. J. 104:603, 1952.

49. Zellermayer, J.: Syphilis in Inductees, U. S. J. Ven. Dis. Inf. 26:194, 1945.

50. Moore, J. E., and Mohr, C. F.: Biologic False Positive Serologic Tests for Syphilis: Type, Incidence, and Cause, J. A. M. A. 150:467, 1952.

51. Stokes, J. H., and James, G. W.: The Problem of the "Biologic False" or Nonspecific Positive Serologic Test for Syphilis: Clinical Observations and Case Studies, Am. J. Syph. 33:114, 1949.

52. Murphy, J. P.: Cerebral Infarction in Migraine, Neurology 5:359, 1955.

53. Ameli, N. O., and Ashby, D. W.: Non-Traumatic Thrombosis of the Carotid Artery, Lancet 2:1078, 1949.

54. Shapiro, S. K., and Peyton, W. T.: Spontaneous Thrombosis of the Carotid Arteries, Neurology 4:83, 1954.

55. Keele, C. A.: Pathological Changes in the Carotid Sinus and Their Relation to Hypertension, Quart. J. Med. 2:213, 1933.

56. Dörfler, J.: Ein Beitrag zur Frage der Lokalisation der Arteriosklerose der Gehirngefässe mit besonderer Berücksichtigung der Arteria carotis interna, Arch. Psychiat. 103:180, 1935.

Hexosamine Excretion in Urine During Pregnancy

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Hexosamines * are important chemical constituents of connective tissue, plasma, and urine. As such, they play an important role in the pathogenesis of rheumatic diseases. It has been observed that the concentration of hexosamines is increased in nodules obtained from patients with rheumatic fever [1] and in the serum of patients with rheumatic fever, rheumatoid arthritis, and disseminated lupus erythematosus.† It has also been observed that the rate of excretion of hexosamines in urine may be increased in patients with rheumatoid arthritis.[4]

Since it is well known that pregnancy can alleviate the symptoms of rheumatoid arthritis, it was considered of interest to study the rate of hexosamine excretion in urine during pregnancy.

Materials and Methods

Urine samples were collected from normal women, pregnant women, and a group of postpartum cases. After each person had been given careful instructions on the method of collecting a 24-hour urine specimen, they were given a collection bottle and told to complete the collection on the morning of their visit to the obstetrical clinic. One hundred thirteen specimens were obtained from 39 pregnancies; nine postpartum and eight normal specimens were also obtained. The age range for all subjects was from 17 to 34 years. The pregnancy group had a mean age of 24.5 years. All patients had routine blood pressure, urine, serological, and general physical examinations. Only specimens from normal uncomplicated cases are included here.

All specimens were brought to the laboratory within a few hours after completion of the collection. The volume and specific gravity of each urine specimen was measured. If the specific gravity and volume of a 24-hour specimen were at great variance from expected values, the patients concerned were carefully questioned as to the manner of their collection. Only in those cases in which it was established that the collection was inaccurate were the specimens discarded. Aliquots were then either placed in a Deepfreeze or hydrolyzed the same day.

In one experiment 10 ml. aliquots of several different samples were dialyzed at 4 C in a beaker containing 4 liters of distilled water. At the end of 24 hours the volumes of the samples in the bags were measured and aliquots taken for hydrolysis.

In all instances, 1 ml. aliquots of urine were hydrolyzed with 1 ml. of 4 N hydrochloric acid for five hours at 100 C. Aliquots of the hydrolyzates were then passed through columns of a sulfonated polystyrene exchange resin (Dowex-50). The hexosamines isolated were subsequently determined by a modification of the method of Elson and Morgan.[5] Urine hexosamine values are expressed as milligrams excreted per 24 hours.

Results

Changes in the rate of excretion of urinary hexosamines during pregnancy are shown in Figure 1. Of the pregnant women, there were 3 observations during the first trimester, 29 observations during the second trimester, 72 observations in the third trimester, and 9 observations in the postpar-

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From the Research Division, Department of Laboratories, Norwalk Hospital.

* The two naturally occurring hexosamines are glucosamine and galactosamine. The method used here does not distinguish between these two amino sugars.

† References 2-4.

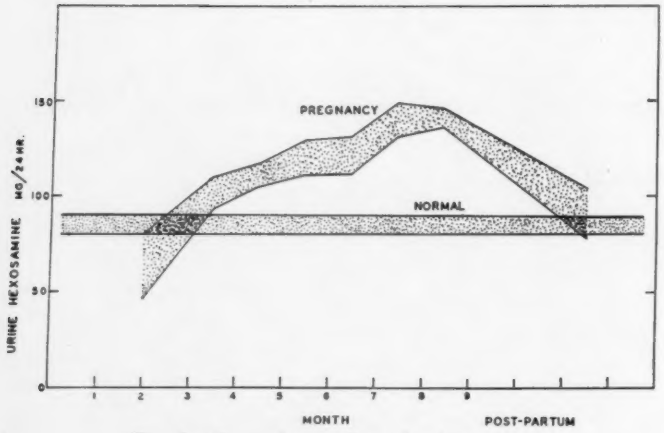

Fig. 1.—Rate of excretion of urinary hexosamine in normal and pregnant women. Stippled areas refer to S.E. of mean.

tum period. The mean postpartum follow-up period was 42 days. It can be seen that the rate of excretion of hexosamines in urine gradually increased during the gestation period, reaching a peak of approximately 140 mg/24 hours at the eighth month. Following delivery the values returned toward normal.

In the second experiment specimens from 11 patients in the third trimester were selected at random. Total hexosamine determinations were performed on these samples before and after dialysis. These values were compared with those obtained from eight normal urine specimens. The data are presented in Figure 2. The total mean 24-hour urinary hexosamine output is expressed as the summation of its dialyzable and nondialyzable components. The total mean excretion in the normal group was 79 mg. per 24 hours, whereas the total mean excretion in the pregnant group was 160 mg. per 24 hours. Of these totals, the normal urines contained 47% dialyzable hexosamine compounds, and the urines from the pregnant group had 44% dialyzable hexosamine compounds. Therefore it was apparent that the increase in total urinary excretion as seen in the third trimester of pregnancy was due to increases of both dialyzable and nondialyzable fractions.

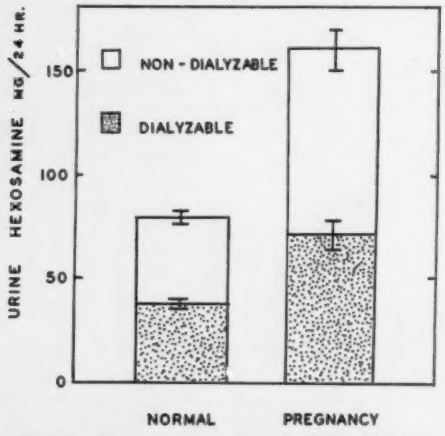

Fig. 2.—Rate of excretion of dialyzable and nondialyzable hexosamine compounds in normal and pregnant women during the third trimester. The vertical lines refer to S.E. of mean.

Comment

Hexosamines are normally excreted in urine at the rate of 70-90 mg. per 24 hours. Hexosamines do not exist in a free state biologically, but as constituents of higher molecular weight compounds. Little is known concerning these hexosamine compounds in urine. It has been noted by several investigators that a large portion (50%-55%, as shown here) of the total urine hexosamine is present in the form of high

molecular weight mucoproteins.‡ With the development of an ion-exchange method for purifying urine hydrolyzates, it has become possible to study other fractions in the urine.§ With this technique and dialysis studies it has recently been shown that 45%-50% of the total hexosamine in urine is present in the form of low molecular weight compounds.[9] The use of gradient elution techniques on cellulose columns has led to the identification of at least three groups of these dialyzable hexosamine compounds.[10]

It is not clear what the significance of increased hexosamine excretion during pregnancy means. Since the changes actually parallel those seen in some cases of rheumatoid arthritis, interpretation of these results will depend a great deal on more precise characterization of these urinary hexosamine compounds.

The source of urinary hexosamine compounds is unsettled. Some of the higher molecular weight mucoproteins may be produced by the lining cells of the genitourinary tract. The low molecular weight hexosamine-containing compounds are more likely excreted or filtered by the kidneys, for they have recently been identified in plasma and other body fluids.[10]

Summary

The rate of urinary excretion of hexosamines was studied in pregnant women and during the postpartum period. It increases during the early months of pregnancy, reaching a peak at about the eighth month; thereafter it returns toward normal.

This increase as studied in the third trimester represents an increase in both the dialyzable and nondialyzable hexosamine compounds.

Dr. Harry Trambert and Mrs. Agnes Cloud helped in obtaining specimens from the Obstetrical Clinic of the Norwalk Hospital. Miss Dorothy Skoglund and Mr. David Fortuna gave technical assistance.

‡ References 4 and 6-8.

§ References 4 and 5.

REFERENCES

1. Consden, R.; Glynn, L. E., and Stanier, W. M.: A Chemical Examination of Connective Tissue in Rheumatic Fever, Biochem. J. 55:248, 1953.

2. Rosenberg, C., and Schloss, B.: Plasma Hexosamine Levels in Acute Rheumatic Fever, Am. Heart J. 38:872, 1949.

3. Boas, N. F., and Soffer, L. J.: The Effect of Adrenocorticotropic Hormone and Cortisone on the Serum Hexosamine Level in Acute Disseminated Lupus Erythematosus, J. Clin. Endocrinol. 11:39, 1951.

4. Boas, N. F.; Bollet, A. J., and Bunim, J. J.: Effect of Acute Clinical Stress on the Levels of Hexosamine in Serum and Its Excretion in Urine, J. Clin. Invest. 34:782, 1955.

5. Boas, N. F.: Method for the Determination of Hexosamines in Tissues, J. Biol. Chem. 204:553, 1953.

6. Tamm, I., and Horsfall, F. L., Jr.: A Mucoprotein Derived from Human Urine Which Reacts with Influenza, Mumps, and Newcastle Disease Viruses, J. Exper. Med. 95: 71, 1952.

7. Hamerman, D., and Hatch, F. T.: Urinary Levels of Mucoprotein Components in Normal Male Subjects, Proc. Soc. Exp. Biol. & Med. 89:279, 1955.

8. King, J. S., Jr., and Hyder, N.: A Glucosamine Conjugate Occurring in Human Urine, Proc. Soc. Exp. Biol. & Med. 89:342, 1955.

9. Boas, N. F.: Low Molecular Weight Hexosamine-Containing Compounds in Urine, Proc. Soc. Exp. Biol. & Med. 92:122, 1956.

10. Boas, N. F., to be published.

MEDICAL MANAGEMENT OF ADRENALECTOMY AND HYPOPHYSECTOMY

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Bilateral adrenalectomy or hypophysectomy will induce objective remissions in some patients with metastatic breast cancer. It is the purpose of this report to detail our methods for managing patients subjected to these procedures. These methods are based on clinical experience and physiological studies of over 200 patients submitted to either adrenalectomy or hypophysectomy. We shall attempt to describe the general medical management for both procedures and to suggest specific methods for handling the problems peculiar to patients with metastatic disease.

Huggins and Scott,[1] in 1945, reported the initial experiences with bilateral adrenalectomy in four patients with advanced prostatic cancer. With the use of desoxycorticosterone and adrenal cortical extract they were unable to maintain life in their patients, although one patient survived almost four months. Subsequently, Green and co-workers[2] successfully managed adrenalectomy in a diabetic patient with the use of large amounts of adrenal cortical extracts. With the availability of cortisone, several investigators demonstrated that adrenalectomized patients could be readily maintained with this hormone. Bergenstal and Dao[3] described their regimen for adrenalectomy, which included the use of desoxycorticosterone and cortisone. Subsequently, Hollander and co-workers[4] demonstrated that cortisone alone was adequate replacement therapy both during surgery and for long-term replacement.

Steroid Replacement

It has been obvious that the cornerstone of management of adrenalectomy or hypophysectomy is adequate dosage of cortisone. There are many ways of ensuring this. Our practice has been to give 50 mg. of cortisone intramuscularly every two hours in six doses the afternoon before surgery to provide a depot of cortisone throughout surgery. The patient is given an additional 100 mg. of cortisone by mouth the morning of surgery.

This schedule has been varied in many ways for certain experimental purposes. Adrenalectomy has been performed using intravenous hydrocortisone at the rate of 20 mg/hour, starting at the time of removal of the second adrenal. Hypophysectomies have been performed using intravenous corticotropin (ACTH), 12.5 mg/liter, at the rate of 100 ml/hour. This last group of patients did not include any whose adrenal glands had been previously suppressed by cortisone or by pituitary destruction. It is to be reemphasized that any regimen will be successful if it provides an adequate amount of cortisone throughout the period of operative and postoperative stress.

After either hypophysectomy or adrenalectomy, cortisone is given intramuscularly, 50 mg. every four hours. This is gradually

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Dr. B. S. Ray, Dr. C. D. West, and Dr. J. P. Maclean collaborated and assisted in this work.

From the Division of Clinical Investigation, Sloan-Kettering Institute for Cancer Research; Medical Service, Memorial Center; and Sloan-Kettering Division, Cornell University Medical College.

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decreased in a week or 10 days to an average of 62.5 mg. of cortisone daily by mouth after adrenalectomy and 37.5 mg. after hypophysectomy.

It has not been necessary to use desoxycorticosterone postoperatively, as effective sodium retention is noted with these doses of cortisone. The urinary sodium loss in the postoperative period has varied between 5 and 20 mEq/24 hours.

In the long-term maintenance of the patient after adrenalectomy, we have heretofore used cortisone only with instructions to use salt liberally. After discharge, the patients are asked to weigh themselves daily and to report any marked weight changes. This will provide a simple gauge of the adequacy of the salt intake. These patients are normal with respect to the metabolic indices which have been measured, namely, insulin tolerance, glucose tolerance and excretion of a water load. Total exchangeable sodium has been within the normal range in these patients, although the mean exchangeable sodium is lower than in a normal group. During the summer months, some patients require supplemental salt tablets. Only two patients were unable to maintain salt balance without a specific salt-retaining hormone. These patients received desoxycorticosterone, 2 mg. Linguets.

We were reluctant to use desoxycorticosterone routinely by injection because of the additional hazards of sodium retention. However, with the advent of the fluorinated steroids, a regimen containing fludrocortisone in low dosage, e. g., 0.1 mg. daily in addition to cortisone, as suggested by Kupperman,[5] may provide optimal replacement and obviate the necessity for the high salt intake.

After hypophysectomy in a patient with intact adrenals, no supplemental salt-retaining hormone is necessary, as the adrenal gland continues to secrete aldosterone in response to sodium restriction, permitting sodium balance with a low salt intake.[6] Thus, these patients are maintained on 37.5 mg. of cortisone or 10 to 15 mg. of prednisone (Meticorten) daily and an unrestricted diet.

Either the adrenalectomized or the hypophysectomized patient on this regimen may regain normal vigor. Many of these patients have returned to activity as housewives or in business. A cooperative patient who is carefully instructed will be able to give the physician ample warning before the occurrence of acute adrenal insufficiency or sodium depletion, so that these potentially dangerous situations have not proved so in the care of these patients. The patients are warned that infection or trauma requires extra cortisone and consultation with the physician.

Fluids and Electrolytes

As noted above, there is no need for saline following either surgical procedure, unless there is extrarenal salt loss. After adrenalectomy, 5% dextrose in water is given intravenously at a rate of 75 ml/hour, and the urine output is watched carefully. The ordinary postoperative oliguria may persist through the second day, and overhydration should be avoided. Oral fluids and feedings are resumed as soon as practicable.

After hypophysectomy, 5% dextrose in water is infused at a rate of 100 ml/hour. It is rare to find oliguria. However, diabetes insipidus can develop with startling rapidity and severity. For this reason, the patients are routinely catheterized and the urine output measured every two hours. When the output reaches a level of 150 ml/hour, the doctor is notified. To control this diabetes insipidus, we usually order 3 units of vasopressin (Pitressin) tannate in oil. Should this fail to affect the polyuria, the same dose may be repeated. In only one patient was it necessary to use vasopressin intravenously to control polyuria.

Following the acute effects of hypophysectomy, the polyuria may vary in degree. If it does not inconvenience the patient, no substitution therapy is required. In others, vasopressin tannate in oil, 3 to 5 units intramuscularly every two to five days, or the use of posterior pituitary powder three to

four times a day, has provided adequate control of the diabetes insipidus.

As the patient following either surgical procedure is usually able to eat by the third postoperative day, potassium supplementation has not been essential. Should alimentation be delayed, however, potassium chloride is given intravenously, 40 to 60 mEq/day.

Antibiotics

The adrenalectomy cases have received procaine penicillin after surgery. Following hypophysectomy antibiotics are used only for specific reasons—the two commonest being pulmonary disease with superimposed infection and opening of the frontal sinus during operation. In over 100 transfrontal hypophysectomies, there has been no case of meningitis or wound infection.

Analgesia

Following adrenalectomy the patient is given the ordinary postoperative analgesics, such as meperidine (Demerol). After hypophysectomy the patient is better treated with codeine, 60 mg. hypodermically. A word of caution is necessary—one must be prepared to ignore an older precept of neurosurgeons, "no morphine in head cases" if the patient has previously been receiving large doses of narcotics. It is wise to continue the narcotics at almost the same level, as withdrawal symptoms can be easily confused with intracranial complications or adrenal insufficiency.

Ambulation

After adrenalectomy, patients are allowed to dangle their feet with assistance on the first postoperative day. Activity is then gradually increased. After hypophysectomy, ambulation is rarely a problem, and the patients are usually permitted to walk to the bathroom on the second postoperative day.

The following is a copy of the orders for the "average" patient after hypophysectomy:

1. Bed rest—position of comfort
2. 5% dextrose in water I.V. to run at 100 cc/hour
3. Water P. O. postnausea
4. Cortisone acetate, 50 mg. I. M. q. 4 h.
5. Dephenylhydantoin (Dilantin), 0.2 gm. q. 8 h. per rectum*
6. Codeine, 60 mg. Ⓗ q. 3-4 h. p. r. n. pain or headache
7. Acetylsalicylic acid, 15 grains (1 gm.) per rectum for fever over 103 F
8. Chart pulse, temperature, B. P. q. h.; notify physician if B. P. over 160 or below 90; notify if temperature 103 F or higher
9. Indwelling urinary catheter
10. Chart urine output q. 2 h.; notify physician if urine output is over 300 cc. in any 2-hour period

Hypothyroidism

After complete hypophysectomy, the onset of chemical hypothyroidism is prompt.[7] The I^{131} uptake and the serum protein-bound iodine fall to myxedema levels. A majority of the patients evidence signs and symptoms of hypothyroidism at two months, although these may be delayed for six months. A thickened, dry skin or obesity have been the earliest signs. We have preferred to wait until these develop before giving thyroid replacement in order to evaluate the completeness of the hypophysectomy.

Replacement has been easy, as there have been no complications when the full dose of thyroid is given initially. Thus, 120 mg. to 180 mg. of desiccated thyroid has usually been adequate. We have occasionally used triiodothyronine (Cytomel) in a dose range of 50 to 100γ daily in divided doses with prompt effect and good maintenance.

Preoperative Evaluation and Management of Specific Problems

The philosophy of medical-surgical evaluation in patients with metastatic cancer differs sharply from routine presurgical evaluation. We do not deny the potential benefits of ablative surgery to any patient if there is a reasonable chance of survival. With this philosophy the 30-day mortality has been

* This is given for the first week after operation at this level or 0.1 gm. q. 6 h. P. O. on the advice of our neurosurgical colleagues.

4% for adrenalectomy and 9% for hypophysectomy.

The several preoperative problems will be discussed separately and in some detail.

1. *Hepatic Involvement.*—Metastatic liver disease which has progressed to the point of causing symptoms, such as anorexia or vomiting, contraindicates surgery. Jaundice is also an absolute contraindication to surgery. These patients do not do well postoperatively and in our experience have not benefitted from surgery. However, patients with hepatomegaly on the basis of metastatic disease, without the above problems, have gone through surgery easily, and in a few cases remission has been achieved.

2. *Pulmonary Involvement.*—Pulmonary parenchymal metastases are often a major problem in these patients. Adrenalectomy in a patient with seriously compromised pulmonary reserve can be performed, but the risk is great. Preoperatively, high doses of cortisone (200-300 mg. daily) for two to three weeks may favorably modify the situation and allow surgery to be performed. The mechanism of action is probably a suppressive effect on both the metastases and on the associated inflammatory process. During this period of cortisone administration, superimposed pulmonary infection should be actively treated. A bronchospastic element is often present in lymphangitic spread and may respond to bronchodilators.

Hypophysectomy can be performed in these patients with considerably less difficulty due to the relative lack of interference with pulmonary function postoperatively.

Following adrenalectomy, careful attention needs to be paid to tracheobronchial toilet. Occasionally tracheostomy has been performed to ensure adequate suction.

3. *Hypercalcemia.* — This results from rapid osteolysis by metastatic tumor. Surgery is risky in the presence of hypercalcemia, and every effort should be made to correct this. Forcing fluids by mouth or intravenously to ensure a urinary output of at least 3000 cc. a day will often lower the serum calcium towards normal. Should this fail, high doses of cortisone may accomplish inhibition of tumor growth and in so doing lower the serum calcium.

4. *Myelophthisic Anemia.*—This is a frequent complication of metastatic mammary carcinoma. Patients with platelet counts above 50,000 per cubic millimeter have under gone adrenalectomy or hypophysectomy without excessive bleeding. When there are evidences of thrombocytopenia, such as petechiae or ecchymoses, surgery may still be performed successfully but excessive bleeding may occur. Transfusions of fresh whole blood are indicated when this happens.

Blood volume determinations are particularly valuable before adrenalectomy. An effort is made to correct any deficiencies before surgery. The preparation for hypophysectomy need not be so elaborate, and a hemoglobin value of 10.0 gm. per 100 cc. has proved adequate for successful surgery.

5. *Miscellaneous.*—Abnormal collections of fluid, such as pleural or pericardial effusions, are drained before surgery. The occasional case of cardiac failure or arrhythmia is treated in the usual manner. Increased intracranial pressure or intracranial metastases are definite contraindications for hypophysectomy, but extensive skull metastases do not interfere with the operation.

Postoperative Complications

1. *Adrenal Crisis.*—This has occurred rarely when the patient has received adequate dosages of cortisone. The diagnosis is made by clinical impression and is based on the occurrence of hypotension, hyperthermia with temperature often to 104 F, vomiting, and weakness. Serum chemistries and eosinophile counts are not helpful. It is obvious that these signs and symptoms are scarcely specific, particularly in a postoperative patient. However, with these symptoms in the absence of obvious bleeding, we prefer to treat the patient with 100 mg. of hydrocortisone in 500 cc. of dextrose in water intravenously over a four- to five-hour period. During this time a blood volume can be done and blood cross matched if necessary. When acute adrenal insuffi-

ciency has occurred, the response to this therapy is dramatic and easily demonstrable within three hours.

2. *Postoperative Hemorrhage and Reduced Blood Volume.*—Four patients in the adrenalectomy series manifested evidence of retroperitoneal hemorrhage and needed transfusions postoperatively. None of the hypophysectomized patients has needed blood postoperatively. Following adrenalectomy, there may be clinical evidence of reduced blood volume manifested by tachycardia, falling blood pressure, and other classical symptoms of shock. The difficulty of distinguishing this from adrenal crisis has been discussed (see above).

3. *Shock Due to Deficiency of Vasopressor Substances.*—Two cases have been seen who following adrenalectomy developed hypotension. Intravenous hydrocortisone and blood did not improve the situation. Levarterenol (Levophed) was then started and resulted in good clinical response. The levarterenol was gradually discontinued in eight hours, and the blood pressure was then maintained.

4. *Electrolyte Disturbances.*—These are usually iatrogenic and have been mild. Hypokalemia and alkalosis have not occurred. The occurrence of a low serum sodium has been traced to overhydration in the immediate postoperative period following adrenalectomy. Hypernatremia following hypophysectomy has not been seen, due to careful observation of urinary output until the time when the patient is fully able to care for his own fluid needs.

5. *Intracranial Complications.*—These are not in the internist's domain, but he must be fully aware of them. Such phenomena as alterations in state of consciousness, slow pulse, and rising blood pressure demand neurosurgical consultation.

6. *Other Problems.*—Occurrences such as pneumonia, atelectasis, and thrombophlebitis are handled as with any other patient. In the presence of any of these complications, the cortisone dosage should not be lowered too rapidly, and adrenal insufficiency must be considered with any sudden deterioration occurring in the postoperative period. Wound healing has proceeded normally in the presence of large amounts of cortisone.

Summary

The management of patients after adrenalectomy and hypophysectomy are discussed from the point of view of the internist. It appears obvious that these procedures demand active collaboration of surgical and medical services from the preoperative period throughout the period after surgery. After surgery the patient needs to be instructed in the necessity of taking cortisone much as the diabetic needs to be instructed about insulin.

With a well-informed patient, the follow-up care is not difficult. The requirements are a cooperative patient and a physician with a basic understanding of endocrinology and physiology.

REFERENCES

1. Huggins, C., and Scott, W. W.: Bilateral Adrenalectomy in Prostatic Cancer: Clinical Features and Urinary Excretion of 17-Ketosteroids and Estrogen, Ann. Surg. 122:1031, 1945.

2. Green, D. M.; Nelson, J. N.; Dodds, G. A., and Smalley, R. E.: Bilateral Adrenalectomy in Malignant Hypertension and Diabetes, J. A. M. A. 144:439, 1950.

3. Bergenstal, D. M., and Dao, T. L. Y.: Management of Addison's Disease in Adrenalectomized Patients, Bull. New York Acad. Med. 29:295, 1953.

4. Hollander, V. P.; West, C. D.; Whitmore, W. F., Jr.; Randall, H. T., and Pearson, O. H.: Physiological Effects of Bilateral Adrenalectomy in Man, Cancer 5:1019, 1952.

5. Kupperman, H. S., and Epstein, J. A.: Oral Therapy of Adrenal Cortical Hypofunction: Use of Combined Fludrocortisone Acetate and Hydrocortisone, J. A. M. A. 159:1447, 1955.

6. Maclean, J. P.; Li, M. C.; Lipsett, M. B.; Ray, B., and Pearson, O. H.: The Physiological Role of Adrenal Salt Hormone (Aldosterone) in Man, J. Clin. Invest. 34:951, 1955.

7. Li, M. C.; Rall, J. E.; Maclean, J. P.; Lipsett, M. B.; Ray, B. S., and Pearson, O. H.: Thyroid Function Following Hypophysectomy in Man, J. Clin. Endocrinol. 15:1228, 1955.

Progress in Internal Medicine

INFECTIOUS DISEASES

Annual Review of Significant Publications

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IN THE PAST year, as in preceding ones, interest in antibiotic agents dominated in the field of infectious disease. No striking advances in knowledge were made, but much thought was given to untoward effects caused by antibiotic therapy especially when it is applied indiscriminately. Many new agents were reported on, but, except for special purposes, none gave promise of excelling the ones now available. A new journal, *Antibiotic Medicine*, appeared in addition to *Antibiotics and Chemotherapy*, now in its sixth volume. Because of antibiotic therapy, the number of publications about tuberculosis have increased, while those on lobar pneumonia have almost disappeared.

Research on viral diseases, against which antibiotics have no influence, led to significant advances in knowledge. Great progress was made in the etiology of minor infections of the respiratory tract by the discovery of a number of related causal viruses. New enteric viruses of undetermined significance also were isolated. Controversy about the merits of immunization against poliomyelitis, measles, and influenza continues.

A statistical report of a life insurance company shows a record low mortality rate from infectious diseases during 1955. The death rate from tuberculosis was 8 per 100,000 policyholders, which is 10% less than in 1954 and 96% lower than in 1911. The mortality from measles, scarlet fever, pertussis, and diphtheria remained at the all time low rate of 0.3 per 100,000 as compared with 58.9 per 100,000 in 1911.[1]

Submitted for publication April 23, 1956.

Antibiotics (Antimicrobics)

Extensive reviews and discussions found elsewhere make it unnecessary to cover most of the publications on the subject of antimicrobics made during the past year. A few significant items merit comment.

In 1953, American manufacturers made 372 tons of penicillin, 187 tons of streptomycins, and 209 tons of broad-spectrum antimicrobics. In 1943, 100,000 units of penicillin sold for $20; in 1953, for 2¢. Of nearly 4000 known antimicrobics, only the following are listed by Welch as useful, in their order of introduction: penicillin, tyrothricin, streptomycin, bacitracin, chloramphenicol, polymixin, chlortetracycline, neomycin, fumagillin, oxytetracycline, viomycin, erythromycin, carbomycin, and tetracyline. In a list of diseases amenable to antimicrobics, question may be raised about the inclusion of leptospirosis, infectious mononucleosis, and viral pneumonia.[2] Semantically, the word antimicrobic is preferable to antibiotic when applied to substances which attack microbes, not life in general. It is hoped also that penicillin will be dispensed and prescribed in milligrams rather than units, in line with other antimicrobics.

Penicillin.—In a symposium on infections, Garrod commented on the absurd number of 47 different dosage forms of penicillin. He agreed with others and myself that about 90% of antimicrobics prescribed is wasted on undiagnosed diseases, for trivial illness, for unnecessary prophylaxis, and in self-medication.[3] Such procedures not only are useless and wasteful but dangerous and a disservice to the patient and to the community. A new form, penicillin V (phenoxymethyl penicillin) was introduced. When given orally, larger amounts appear in the blood than after similar doses

of penicillin G.* Two patients with subacute bacterial endocarditis were treated successfully with doses of 12,000,000 units (7500 mg.) daily for six weeks.[6] It is dispensed in milligrams and units. Preparations of penicillin for administration by inhalation, troches, and ointments were omitted from the 15th revision of the "U.S. Pharmacopeia" because of the danger of sensitization and superinfection with their use.[7] One might add, because of their low effectiveness. If topical therapy is desired, it may be better to use agents like neomycin or polymixin, which are too toxic for parenteral injection and if applied locally do not sensitize patients to drugs which at some later time may be needed for a serious systemic infection. According to a conjecture, over 1000 fatalities have occurred in the United States from anaphylactic reactions to penicillin. Cow's milk, after the animal is treated with penicillin for some infections, may serve as a factor of sensitization.[8] Traces of penicillin were found in 3% to 11.5% of samples of milk tested at random.[9]

Skin tests are unreliable to detect hypersensitivity to penicillin. The incidence of dangerous reactions can be minimized by giving penicillin only when it is necessary and by substituting other antimicrobics if the patient has an allergic background.[10] In a patient highly sensitive to penicillin an allergic reaction cannot be prevented by antihistamines. Epinephrine still is the drug of choice for the treatment of reactions. Changing the brand of penicillin is not likely to solve the problem.[8]

Hemolytic streptococci embedded in agar in the animal body were protected from phagocytosis, but were killed when penicillin was injected five hours later. Penicillin given after 12 hours, when the cocci no longer were multiplying, failed to sterilize the foci. The experiments reemphasize the importance of thorough early treatment and explain the futility of prolonged treatment in certain long-standing infections.[11]

*References 4 and 5.

Bacterial Resistance to Penicillin.—Other factors besides the formation of penicillinase contribute to the development of bacterial resistance to penicillin, as follows: (*a*) Some bacteria degrade penicillin after it enters the cell; (*b*) resistant strains bind less penicillin than sensitive ones; (*c*) antimicrobic-resistant variants of sensitive parent bacteria combine with penicillin as do the parent strains but are not killed.[12]

Finland,[13] Dowling,[14] Lepper,[15] and Clough[16] reviewed the subject of the development of bacterial resistance to antimicrobics, especially in regard to staphylococci. The problem now is how best to conserve the effectiveness of antimicrobics which still are active against staphylococci. The most fundamental measure would be to curb indiscriminate antimicrobic therapy. In the opinion of one group of observers, the incidence of penicillin-resistant staphylococci in hospital patients is roughly proportional to the amount of penicillin used in hospitals.[17] Alarming evidence is accumulating that among hospital patients staphylococcal infections now are the chief causes of death due to bacterial disease. In one institution, necropsy revealed 5 deaths caused by staphylococci in 1950 and 87 in 1954. Most of the strains were antimicrobic-resistant.[18]

The prospect of finding a new antimicrobic to attack staphylococci resistant to the agents now in use is not promising. Several will be cited later. To preserve the present effectiveness of erythromycin against staphylococci, the government of New Zealand has restricted its use to the treatment only of appropriate diseases. There is good reason for the edict, but governmental interference in medical affairs was questioned.[19] Perhaps the use of novobiocin also needs restriction for the same purpose.

Fortunately, α-hemolytic (viridans) streptococci have not become resistant to penicillin according to tests on strains obtained from patients with endocarditis between 1944 and 1954.[20]

Other Antimicrobic Agents.—In an extensive review of 564 papers, Finland discusses the emergence of antimicrobic-resistant bacteria.[21] Another essay concerns the changing patterns of resistance. No important changes of resistance have been authenticated, in his opinion, for pneumococci, Group A hemolytic streptococci, meningococci, gonococci, Hemophilus influenza, or Proteus bacilli. The use of combinations of antimicrobic substances may delay and depress the emergence of resistant bacteria in cultural studies, but in practice this has been demonstrated only in patients with tuberculosis.[13]

The report of a symposium on antimicrobic therapy appeared in the August, 1955, issue of the *Annals of Internal Medicine.* Yow regards sulfonamide compounds to be less potent than antimicrobics of fungal origin, but they also cause less drastic changes in the normal flora and fewer subsequent superinfections. Sulfonamide compounds are effective in the treatment of meningococcal infections, bacillary dysentery, chancroid, and trachoma. Sulfanilamide, sulfathiazole, and sulfaguanidine were omitted from the 15th revision of the "U.S. Pharmacopeia."

According to Weinstein, the prophylactic use of antimicrobics did not prevent the appearance of pneumonia or otitis during measles. The procedure increased the risk of bacterial complications.[22] Similar observation was made by Watson.[23]

Bacitracin for parenteral use is available. A single dose of 25,000 units or a total daily dose of 100,000 units should not be exceeded. Bacitracin is said to be useful for infections caused by cocci and clostridia resistant to penicillin and tetracycline.[24]

Altemeier outlines methods for the prevention and treatment of infections in surgical practice.[25] Prophylactic use of antimicrobics is of value in (1) surgery in contaminated areas, such as the gastrointestinal tract, respiratory tract, and urinary tract, (2) contaminated wounds of violence, (3) surgery in the presence of associated derangements of the urinary tract, (4) emergency surgery in the presence of unrelated infections, such as acute streptococcal sore throat, (5) injuries or operations in the oropharynx, and (6) coexisting valvular heart disease. Methods for controlling infections after a catastrophic atomic explosion were outlined. Oral therapy with broad-spectrum antimicrobics would be most practicable. Polymixin B is the agent of choice for the treatment of infections with Pseudomonas aeruginosa. The dose should not exceed 200 mg. per day.

Gram-negative bacilli, especially of the Aerobacter and Proteus group, apparently have developed a degree of resistance to streptomycin, chlortetracycline, and oxytetracycline.[26] The genus Proteus is becoming more important as an invader after some other primary infection is treated with antimicrobics. Some varieties of Proteus were sensitive to the tetracycline drugs, others were resistant. Neomycin inhibited most strains. All of them resisted bacitracin, polymixin B, and erythromycin. Since 1949, an increasing number have become resistant to chloramphenicol and to the tetracyclines.[27]

Tests in vitro on 50 strains of meningococci showed no evidence of increasing resistance to penicillin. Six strains were moderately resistant to sulfadiazine.[28] Editorial opinion favors the use of sulfadiazine with chloramphenicol added for meningococcal infection.[29] Penicillin is superior to other agents against gonococci. No evidence of increased resistance was detected. Sulfonamide therapy once led to the development of resistant gonococci, but the incidence of resistant strains has declined from 84% to 19% since sulfonamide therapy was supplanted generally with penicillin.[30]

According to Goldsmith, a relation of vitamin nutrition to resistance against infection is not established. It is uncertain if antimicrobial therapy interferes with the absorption or utilization of vitamins. Therefore it is impossible to state which vitamin, if any, should be administered with which

antimicrobic in the treatment of a given infection.[31]

New Antimicrobics.—Anisomycin is said to be active against protozoa, especially Trichomonas vaginalis and Endamoeba histolytica. Against the latter, fumagillin was more active.[32] Xerosin was active against an encephalitis virus and influenza virus.[33] Florey described experiments with several new antimicrobics derived from a marine fungus. These include a new penicillin which may be effective for the treatment of typhoid, and cephalosporin C, which may attack penicillin-resistant staphylococci.[34] Novobiocin (Albamycin, Streptonivicin, Cathomycin, Cardelmycin) attacks staphylococci, other Gram-positive cocci and Gram-negative bacilli. Staphylococci did not become resistant to vancomycin.[35] Spiramycin[36] and ramnacin[37] also were obtained from Streptomyces.

The formulas of antimicrobics of a polyene group, mycomicin, agrocybin, and diatretyne I were determined. Closely related are nystatin, flavacid, and candidin. These agents and actimycoin, rimocidin, chromin, candicidin, trichomycin, and ascocidin are active chiefly against yeasts and fungi.[38] Fourteen new antimicrobics were reported on at an antibiotics symposium in October, 1954.[39] Coined names for these and the ones mentioned before are evolving a new branch of medical language.

Viral Infections of the Respiratory Tract

Studies made by Huebner, Rowe, Hilleman, and their associates led to great advances in the etiology of minor infections of the respiratory tract, the commonest ailments of mankind. By using new methods of tissue culture, several related adenoviruses were recovered from patients.§ The viruses are epitheliotropic, avirulent for animals, resistant to antimicrobics, and related antigenically. Morphologically their particles are spherical or doughnut-shaped bodies 10 mμ in diameter.[42]

§ References 40 and 41.

The viruses are classified into 14 specific types.[43] Virus Type 3 causes nasopharyngitis and pharyngoconjunctival fever; Types 2 and 3 cause viral pharyngitis; Types 3, 4, and 7 cause acute respiratory disease (ARD) and viral pneumonia.[44] Type 8 is associated with keratoconjunctivitis.[45] Types 1, 5, and 6, commonly found in excised tonsils, have been recovered less often during disease, but are invasive because antibodies found in the blood indicate previous infection. Each of the viruses may cause inapparent infection. They have no relationship to what is called the common cold. It is likely that other undiscovered viruses also cause diseases included with the entities mentioned. Old names, such as colds, coryza, rhinitis, catarrh, sore throat, and grippe eventually will be replaced by terms indicating the causative virus and grouped on an etiologic basis.

The viruses first were isolated from excised adenoids and tonsils and later from patients with minor infections of the respiratory tract. Their possible causal relation to chronic tonsillitis was considered.[46] However, it seems more important to regard their discovery in the pharynx as partly solving an epidemiologic enigma. Their residence in carriers may provide a perpetual source of infection of minor infections of the respiratory tract. A carrier state is likely to exist because the viruses live symbiotically in invaded cells in tissue culture and are liberated in small amounts.[47] By electron microscopy only a small proportion of cells contain virus particles, and these are not readily released.[48] The retention of virus also may explain why some persons exposed to patients do not acquire infection.

Several epidemics of pharyngoconjunctival fever caused by adenovirus. Type 3 were studied. The incubation period was four or five days. Patients had pharyngitis, rhinitis, conjunctivitis, and regional lymphadenopathy. A specific antibody response occurred. Conjunctivitis alone in one patient suggested that the virus may be the cause of one form of conjunctivitis, espe-

cially in adults. Swimming pools are one possible source of infection.†

Virus Types 3, 4, and 7 caused epidemics in widely separated military posts. Patients infected with any one of the three types of virus usually developed antibody against one of the others as well, probably as the result of previous infection. None had antibody for Types 1, 2, 5, or 6 virus. The complement-fixation test is used for routine diagnosis, and the type is determined by the specific neutralization test.[40] In one epidemic, serologic tests revealed infection in 77% of members of one group. One-fourth of the victims were sick enough for hospitalization, and a number of these had viral pneumonia.‡ The proportion of pneumonias to mild disease is the same as in the epidemic I described in 1940.

Ward transmitted infection to volunteers by swabbing their conjunctivas and pharynx with throat washings from patients or with tissue-culture fluids of Types 3 and 4 viruses. Characteristic inflammation, systemic symptoms, and specific neutralizing bodies developed. Viral pneumonia occurred in one subject 17 days after inoculation with Type 3 virus.[53] Huebner transmitted pharyngoconjunctival fever to volunteers, but only to ones whose blood contained no specific antibody.[45] It is curious why these simple procedures have not succeeded in the past.

Type 8 virus was isolated from a patient with signs typical of epidemic keratoconjunctivitis (EKC), a disease rampant in 1942. At that time an agent related to St. Louis encephalitis was implicated, and it may have been a different disease. It is different from follicular conjunctivitis and from the kind present in pharyngoconjunctival fever. Nevertheless, the Type 8 virus isolated from the patient was neutralized by preserved serum from victims of EKC in 1942, but not by antiserums of Types 1 to 7 viruses.[54] An adenovirus was recovered from the feces and lymph nodes of patients with mesenteric lymphademitis.[55]

Vaccine.—As in the case of influenza, the discovery and isolation of the causes of some minor infections of the respiratory tract led to attempts at immunization. Inactivation of Types 3, 4, and 7 viruses with formaldehyde provided a vaccine which evoked specific neutralizing substance and gave protection against experimental infection in inoculated volunteers and during an epidemic among recruits.* The results confirm the relation between the virus and the disease, but the practicability of vaccination is doubtful. The numerous specific types of virus and the short duration of immunity limit the value of vaccination.

Viral Pneumonias.—The tendency persists to regard the nonbacterial pneumonias which occur during epidemics of minor infections of the respiratory tract as complications or as separate entities.[45b] Because cold agglutination did not occur during pulmonary involvement caused by adenoviruses, these pneumonias were excluded from consideration.[56] Yet others found that infection with adenoviruses was responsible for a large proportion of cases of viral pneumonia.§ Cold agglutination is only one feature of certain pneumonias. Even in epidemics, cold agglutinin may appear in only 50% of cases.

It is likely that most viral pneumonias are integral parts of various mild epidemic infections of the respiratory tract and are the severest forms of basic disease spectrums, as I suggested in 1938. In support of this view, viral pneumonia developed in numbers of patients during epidemics of mild disease caused by adenoviruses‖ and in inoculated volunteers.[53] A different virus, PAP, was isolated from pneumonia patients in 1944, and ones like it were obtained recently. Cold agglutinin and specific antibody appeared in the blood, and no cross reaction occurred with adenoviruses.[58]

Now that (*a*) the causative agents of some forms of viral pneumonia have been isolated, cultivated, and measured, (*b*) spe-

† References 49-51.

‡ References 44 and 52.

* References 45 and 45a.

§ References 52 and 57.

‖ References 44, 52, and 57.

cific immunity develops, (*c*) vaccination modifies infection, and (*d*) the disease can be transmitted by the inoculation of secretions from patients or cultures of virus, Koch's postulates are more than fulfilled. It is time to abandon the ambiguous term "primary atypical pneumonia."

None of the broad-spectrum antimicrobics influenced viral pneumonia in 55 patients in Sweden.[59] Viruses are resistant to antimicrobics, and it is hard to account for the beneficial results from antimicrobic therapy of viral pneumonia previously reported by competent observers. Perhaps the pneumonias were of other origin or were caused by secondary bacterial infection.

Psittacosis.—Attention is called to the ease with which psittacosis may be mistaken for banal mild or severe infection of the respiratory tract, particularly viral pneumonia. Tetracycline is said to be effective in therapy.[60] Evidence of person-to-person transmission of psittacosis was observed in Denmark, where several examples of probable contact infection occurred.[61]

Influenza.—In one region during an epidemic of influenza A′ in 1953, no B or C viruses were present. In 1954, however, influenza B and C were prevalent. The B virus was so different antigenically from the 1940 Lee B strain that the present B vaccine may not be effective against it.[62] Influenza C infection was common in England and Scotland in 1954.¶ According to Francis, a new serologic type of virus was isolated in Japan. It eventually may be classified as influenza virus D.#

According to Andrewes, the practicability of influenza vaccines, except under special circumstances, is questionable. This idea was repeatedly expressed in these reviews. Specific antibody is almost useless in the blood where there may be no virus for it to neutralize, and antibody imperfectly penetrates the respiratory mucosa where it is needed. In addition, the constant change of antigenic patterns of the virus makes it difficult to select the proper strains for making vaccine against anticipated outbreaks.[67]

Transient viremia occurred in 50% of mice allowed to breathe nebulized influenza virus. The virus attached itself to the erythrocytes.[68] If this occurs in man it may represent a "spilling-over" of virus from the respiratory tract or may account for systemic disease and the formation of antibody.

An influenza virus which reacts to antibody but is not infectious emerged during inoculation experiments in mice. The changed virus did not seem to be a developmental phase of viral synthesis, but probably appeared in an aberrant cycle of multiplication.[69] Influenza B virus was isolated directly in tissue cultures of monkey renal cells.[70] The incorporation of radioactive phosphorus with influenza virus by Liu and his co-workers may provide a new means of investigation.[71] L-Canavanine, an amino acid, inhibited the growth of an influenza virus in egg and tissue cultures. The inhibition was reversed by L-arginine.[72] A synthetic basic polypeptide, polylysine, also inhibited the growth of virus.[73]

Other Viral Diseases

Poliomyelitis.—Further studies were made on the epidemiologic behavior of poliomyelitis. According to Horstmann, poliomyelitis may be as contagious as measles among susceptible members of families. Infection rates for those under 15 years of age were 100% for household contacts and 87% for daily contacts. The ratio of inapparent to overt disease in families was about three to one.[74] In contrast with the high proportion of victims among family contacts is the rarity of poliomyelitis in hospital personnel who attend patients. None of 50 exposed persons in contact with 128 patients became sick.[74a] It was suggested that the low infectiousness of patients by the time they reach the hospital and the precautionary techniques employed were responsible. In other studies, genetic or environmental factors were thought to play a role. The case fatality rate was higher in families with several victims than when single members

¶ References 63 and 64.

References 65 and 66.

had poliomyelitis. Death occurred chiefly in patients over 15 years old among whom bulbar involvement was more common.[75]

Although earlier attempts to implicate animals as a reservoir of infection were inconclusive,[76] investigators by using new techniques were able to demonstrate specific neutralizing bodies for Types 1, 2, and 3 poliomyelitis virus in mature cattle. Weaker antibodies were found in horses, hogs, and chickens.[77] The question arises whether the animals were actually infected and if the ecology of poliomyelitis is analagous to that of other neurotropic viruses which are widespread in various species of animals and birds. Myocarditis was found at necropsy in 14 of 15 patients. In one, acute cardiac disease obscured poliomyelitis until diagnosis was made post mortem.[78]

In attempts to discover chemotherapeutic agents for poliomyelitis, 4-amino-1-naphthol HCl and gallic acid seemed to be effective both prophylactically and in treatment in inoculated monkeys.[79]

Cultures of human fibroblasts infected with poliomyelitis virus were studied cinematographically. After 24 hours round masses appeared in the cytoplasm, increased in size, and pushed the nucleus aside. Vacuolization of the cytoplasm suggested a mode of release of the virus before the cell died.[80]

Two groups of investigators found that in certain conditions, the development of a yellow color evoked in HeLa cell cultures in the presence of phenolsulfonphthalein is prevented by unneutralized poliomyelitis virus. This behavior may provide a method to measure the virus and its specific antibody.* In other tissue cultural studies, cells exposed to Newcastle virus were resistant to the cytopathogenic effect of poliomyelitis virus. Evidently biologic "interference" occurred.[83]

Antipoliomyelitis Vaccine. — Many observers are skeptical of the value of vaccination against poliomyelitis. The initial tests were made in a year when the general incidence of the disease was low. A public health survey reveals a decline of 25% in the incidence of the disease in 1955 as compared with 1954, but it is uncertain how much influence vaccination had in reducing the number of cases.[84] The decline may have been partly a natural one characteristic of epidemic diseases.

On the other hand, the results reported from vaccination generally are favorable. The number of reported cases among 7,000,000 vaccinated children was 25% to 50% below the incidence expected without vaccination.[86] According to Langmuir,[87] the attack rate for paralytic poliomyelitis was two to over five times greater in unvaccinated children. In the Massachusetts outbreak the incidence was 198 per 100,000 in unvaccinated children and 94.5 per 100,000 among those who had received one injection. Both rates were much higher than reported in the early trials in 1954. No secondary infections were noted after contact with patients who developed poliomyelitis after vaccination. There was no evidence that the vaccine caused poliomyelitis.[88]

Whether the modified vaccine now distributed is both safe and effective remains to be seen. Lepine opposes mass vaccination, but recommends it for persons who have little or no demonstrable antibody.[90] According to Gard, it is theoretically impossible to preserve the antigenicity of a completely inactivated virus.[90] There is evidence, however, that inactivated poliomyelitis vaccine viruses give rise to significant amounts of antibody in animals and in volunteers.[91] The amount of antibody after vaccination does not indicate the degree of immunity achieved.[90] If the improved, safe vaccine is immunogenic, it is the first practicable example of a dead viral vaccine able to prevent disease.

A plea for objective evaluation of the vaccination program was published by the American Association of Public Health Physicians.[92]

Further to emphasize the need for a reliable vaccine is a report that studies sup-

* References 81 and 82.

ported by the National Foundation for Infantile Paralysis are under way by Sabin. He will attempt to provide a live virus to be given orally and safely as a vaccine.[94] Evidence is at hand that certain modified poliomyelitis viruses evoke immunity when fed to monkeys and to volunteers without causing viremia or disease.[95] Koprowski fed live attenuated Type 1 and Type 2 viruses to 225 nonimmune persons. All developed homotropic antibody, and none were harmed. Transmission of virus by contact with these persons was observed in 5 of 15 others. The presence of antibody in the blood does not always prevent the establishment of alimentary infection with virus.[96]

In an English community only 4 cases of paralytic poliomyelitis occurred in children previously vaccinated with vaccinia virus, as compared with 21 cases in unvaccinated ones. Perhaps there is an inverse relationship between antismallpox vaccination and paralytic poliomyelitis.[97] The phenomenon of biologic interference may be involved.

Measles.—According to Watson, sulfadiazine acts therapeutically if drug-sensitive bacteria cause secondary infection during measles. When no bacterial infection was present, the administration of sulfadiazine prophylactically was accompanied by more complications than occurred in untreated patients. In view of this finding, he recommends a reevaluation of the attempted prophylaxis against other viral infections.[23] Editorial comment on the subject reads: "Indiscriminate dosing with antibiotics for a disease capable of causing twenty thousand cases a week has nothing to recommend it."[98] It is better to treat bacterial infections as they arise.

During an epidemic of measles in a school, 10 pupils were given 0.1 cc. γ-globulin per pound on the fourth day after exposure; 24 were given 0.02 cc. per pound, and 58 who had had measles were untreated. Six of the 10 who received the larger dose developed measles. Small doses failed to modify the disease in 4 of 19 students. Of those who said they had had measles, 20 of 58 developed the disease. An epidemic of German measles ensued, but γ-globulin neither prevented nor modified the disease.[99] In a British survey, the attack rates of measles in children between 3 and 5 years old who were injected with γ-globulin were from 22% to 67%. In others, who received adult serum, the attack rates were from 69% to 87%.[100] Evidently better means of immunization should be sought.

Over an 18-year period 21 cases of measles encephalitis occurred among nearly 25,000 measles patients, or about one case in 1300 patients. Five died, six have serious sequels, three have mild sequels, and six are well.[101]

Interest in the giant cells of measles was revived. These so-called Alagna cells are present in the bronchi, sputum, and nasal secretion about five days before the dermal eruption. Their presence may serve as a diagnostic aid in the prodromal period.[102]

Mumps.—The virus of mumps can be isolated readily by inoculating tissue cultures of HeLa cells or monkey-kidney cells with patients' saliva.[103] Confusion may result if the monkey cells carry a latent virus of different nature.

Varicella.—Three cases of congenital varicella encountered in an eight-month period suggests that the disease occurs in this form more often than the eight cases reported between 1878 and 1953 would indicate. In the three cases presented, the mothers had varicella or had just recovered from it at the time of delivery. In two infants the eruption was present at birth, in the third, it appeared after 10 hours.[104] An epidemic of chicken pox on a small island in March, 1954, apparently originated from a patient with herpes zoster. Two weeks later, two cases of varicella developed, followed by sporadic ones in June and July. The disease was the same clinically and immunologically as that without known relation to herpes zoster.[105]

Herpes Simplex.—The virus of herpes simplex may be an important cause of meningoencephalitis. In one series of cases, about 5% probably were caused by herpes

virus, 7% by Leptospira, 9% by lymphocytic choriomeningitis, and 12% by mumps virus. No cause could be established in 75% of cases. Complement-fixing antibodies for herpes virus seldom are found in children but are present in the majority of persons over 30, indicating past infection.[107]

In my personal experience, lobar pneumonia in one instance coincided with an extensive herpetic labial and nasal eruption. Several typical features of pneumonia were absent, and the response to penicillin was slow. Resolution was delayed for over a month, as expected if the interstitial tissue were involved. It is possible that herpes virus played a role in the pulmonary lesion.

Coxsackie Virus.—Of 66 patients admitted to a hospital with a diagnosis of poliomyelitis, Coxsackie viruses were isolated from the stools of 14, and neutralizing antibodies were present in their blood.[108] Virus Group B Type 3 caused fatal myocarditis and encephalitis in infants in South Africa.[109] Group A Coxsackie viruses are classified into 19 specific types.[110]

Colorado Tick Fever.—This entity, according to Eklund, is the only tick-transmitted viral disease of man in the Western hemisphere. It is not limited to Colorado, but is present in all of the western States wherein virus-bearing ticks have been found. The virus has been isolated from the blood of 193 patients. Tourists infected in endemic areas developed the disease in Florida, Maine, and New York State. Tick fever, at times, may cause serious encephalomyelitis.[111]

Cat-Scratch Disease.—Kalter and his associates describe the great variability in the clinical manifestations of cat-scratch disease among 250 patients.[112] So many cases collected by one group of observers makes one wonder why the disease was unrecognized until recently. It is unlikely that it is spreading or increasing in incidence; it is being diagnosed more often, perhaps too often. The relationship of the causative agent to the psittacosis-lymphogranuloma venereum group of Miyagawanella is uncertain. The skin test is of value in diagnosis when the signs and symptoms are suggestive. In another study, 7 of 28 veterinarians gave a positive reaction to the skin-test antigen composed of pus from lesions. Four of the seven reactions persisted for 8 to 10 months as a local granulomatous lesion. Veterinarians probably are exposed repeatedly to the infection.[113]

Infectious Mononucleosis.—Presumably a viral disease, mononucleosis rarely occurs as a cross infection in hospital wards or among roommates, nor has it been transmitted experimentally. Hoagland suggests that infection follows intimate oral contact and an exchange of saliva.[114] It ought to be easy to test this assumption by the simple expedient of kissing or, as wags define it, swapping spit.

Yellow Fever.—A report of an informal conference on yellow fever appeared in the July issue of *The American Journal of Tropical Medicine and Hygiene.* The disease was epizootic and epidemic in Panama after 1948 and in Brazil from 1951 to 1953. Mexico soon may be involved. The outbreaks provided opportunity for modern diagnostic study.[115]

A newly recognized clinical feature is the general mildness of the disease. The majority of patients had no jaundice or albuminuria. Yellow fever may be mistaken for dengue, malaria, influenza, leptospirosis, or viral hepatitis unless etiologic studies or hepatic biopsies are made.

It seems now that yellow fever is essentially a primary hepatic disease with renal involvement as a specific hepatorenal syndrome. It may therefore be regarded as the prototype "primary typical viral hepatitis." Luckily, viral hepatitis (infectious jaundice) in contrast was not called primary atypical hepatitis as in a parallel case pertaining to "typical" lobar pneumonia and "primary atypical" or viral pneumonia.

It has been observed in communities that yellow fever and dengue rarely occur at the same time. Biologic interference of one virus with the other may account for the circumstance.[116]

Viral Hepatitis.—In a study of 651 per-

sons, 271 of whom had had acute icteric hepatitis four to seven years previously, none had evidence of advanced disease of the liver ascribable to hepatitis alone. The prevalence of demonstrable severe or active hepatic disease was no higher in those who had had hepatitis than in the others. When mild disturbance was present, other causative factors seemed to be implicated. The development of chronic hepatic disease after viral hepatitis depends on diverse factors. Measurement of the 24-hour excretion of urobilinogen in the urine and of the amount of sulfobromophthalein retained in the blood aids in recognizing nonicteric or clinically inapparent disturbance of the liver.[117] Viral myocarditis was observed in four patients who died from hepatitis.[118]

Opinion is divided about the value of cortisone therapy for the treatment of viral hepatitis. New study suggests that it may hasten recovery.[119] However, in a generally mild, self-limiting disease, it is doubtful if cortisone should be used. It may be helpful in the rare severe case.

The viruses of hepatitis have not been isolated with certainty, yet there has been no objection to naming the disease viral hepatitis. In studies on the problem, inoculation of serum from patients caused no overt changes in embryonated eggs. However, as with the viruses of influenza and mumps, there was an increase in the number of histiocytes in the allantoic fluid as if a virus were growing. The reaction was reversed by γ-globulin and convalescent serum.[120]

Epidemic Hemorrhagic Fever.—Epidemic hemorrhagic fever which rose to prominence during the Korean conflict exists in other parts of the world, as may have been predicted. In addition to the endemic hemorrhagic nephritis of Siberia, similar disease was described under different names from southeastern Russia, Hungary, and Czechoslovakia. It occurs among persons exposed to the dust of grain and to livestock. In all probability the disease or related ones always were present in endemic areas but were unrecognized or confused with other ones. There is no reason to believe that it is spreading. Unusual epidemics of nephritis were observed in recent years in Scandinavia, Yugoslavia, and Bulgaria, but the disease differed clinically from epidemic hemorrhagic fever.†

Equine Encephalitis.—About 11% of 614 persons in Colorado had neutralizing antibodies for western equine encephalitis in their blood. The rate was twice as high in persons under 30 years of age as in older ones.[123] The virus was found in English sparrows, and serologic evidence of previous infection was present in 14% of these pests.[124] Virus also was recovered from New Jersey mosquitoes.[125] In three papers in the January, 1955, issue of *The American Journal of Tropical Medicine and Hygiene*, mites were said to be unimportant in the perpetuation or transmission of equine encephalomyelitis.

Yesnick reviewed reports on 37 instances of involvement of the central nervous system during viral pneumonia and added one of his own.[126]

Rabies.—Hall described the introduction of rabies into communities by stray dogs and the transmission of infection to other dogs and to man. Methods for the prevention and control of rabies were outlined.[127] In addition to rabies virus, another one related to St. Louis encephalitis virus was isolated from bats in Texas.[128]

Viral Dysentery.—An outbreak of "gastroenteritis" occurred in Portland, Ore., in November, 1954. About 200 victims in 71 households were counted, but thousands of cases presumably occurred. None of the common enteric pathogens seemed to be the cause.[129] To show how difficult it is at times to introduce a new idea or a new name, no mention was made in the report of a possible viral cause. The large epidemic, the household incidence, and its autumnal occurrence are characteristic of mild epidemic disease appropriately named viral dysentery (bowel trouble of viral origin).[129a]

Experimental studies on the transmission

† References 121 and 122.

of the infection to volunteers were reviewed by Gordon.[130] Studies on the disease were published in Russian. A virus was said to have been isolated which caused paralysis in infant mice and was neutralized by convalescent serum from patients.[131] It may be a variety of Coxsackie virus or an ECHO virus present as a commensal.

Newly Isolated Enteric Viruses.—Previously unrecognized viruses may be found if sought for or encountered incidental to other studies. From rectal swabs made from 1566 healthy children, 31 cytopathogenic viruses were isolated. Five were poliomyelitis viruses, one a Coxsackie virus, and the rest belonged to a hitherto unknown group.[132] In similar studies of 319 infants in Egypt, 113 carried a recoverable virus. Fourteen were poliomyelitis viruses, and the rest were unknown ones.[133]

Thus far, the new enteric viruses have been classified into 13 antigenic types. They are cytopathogenic in tissue cultures and may be invasive in man because they are neutralized by human γ-globulin. None is known to cause disease. A question of their etiologic significance arises like that concerning a number of neurotropic viruses isolated from animals in Africa against which specific antibodies occur in the blood of natives. Because viruses of both groups are "in search of disease," they were named "orphan viruses." The new ones now are grouped as "enteric cytopathogenic human orphan" (ECHO) viruses. Perhaps one or more of them may cause viral dysentery?

To serve as a clearing house in order to avoid confusion and duplication in classification, a committee was organized to receive and study strains of enteric viruses as they are isolated.[134]

A review of immunizing procedures against viral diseases was published.[135] Investigators of viral disease who deal with explanted animal cells in cultural experiments may be confused if some unsuspected virus is present in the tissues used. Rustigian and his co-workers working with dengue virus encountered an unidentified filtrable agent in monkey renal cells.[136] Chronic murine pneumonia, occasionally present in apparently healthy rats in laboratory colonies, may interfere with studies on infection of the respiratory tract in these animals.[137]

Wesselhoeft's paper about the effect of acute infectious diseases during pregnancy does not lend itself readily to brief review. No other viral disease during pregnancy injures the fetus as rubella does. Pregnancy seems to increase susceptibility to poliomyelitis but does not increase its severity.[138]

Coccal Infections

Group A Hemolytic Streptococci.—During an epidemic of streptococcal infection characterized by pharyngitis, scarlet fever, acute nehpritis, and pyoderma, a new type strain of Streptococcus was isolated. Specific antibody against it was present in the blood of most of the patients. Like Types 12 and 4 streptococci, the new strain was nephritogenic.[139]

Local infection with Type 12 cocci or intravenous injection of filtrates from cultures caused nephritis in rabbits which resembled the disease in man. Albuminuria, hematuria, and hypertension occurred. Since filtrates induce changes like those caused by infection, the nephritogenic substance seems to be extracellular, perhaps as a protein exotoxin. Rabbits recover after the first evidence of nephritis, but the disease recurs after eight weeks. Reinfection makes the resulting changes more severe. Infection with other types of streptococci did not cause nephritis.[140] These experiments are of interest in connection with a streptococcal proteolytic enzyme as a cardiac poison and other experiments on rheumatic fever mentioned later in this review.

After acute attacks of recurrent streptococcal infection, areas of the skin repeatedly infected are more highly sensitized to streptococcal nucleoprotein than unaffected areas. Sensitivity may last for years. When the intervals between attacks are short, reinfection may arise from chronic foci; otherwise attacks may follow infection with

different strains or from other sources. Focal allergic reactions may be provoked by inoculation of streptococci in distant parts of the body.[141]

Experiments with streptococcal pneumonia in rats suggest that infection with a specific type of Streptococcus when treated with penicillin leaves a degree of immunity against infection with strains of other types.[142]

Pneumococcal Infections.—Commercially prepared serums for determining the type of pneumococci are almost unobtainable, yet "typing" is of value diagnostically and epidemiologically. It is gratifying, therefore, to find a paper on pneumonia in which the procedure was used. Type 3 pneumococci caused a higher mortality rate than others despite antimicrobic therapy, especially when concomitant disease, bacteremia, and leucopenia were present and in old age. Recovery is slower from pneumonia caused by Type 2 and Type 3 pneumococci.[143]

In my own experience pneumococcal lobar pneumonia was unexpectedly prevalent in tropical Java. Twenty-seven patients entered the hospital in the rainy season between January and June. Despite an average daily temperature of 85 F, pneumonia in seven began after a wetting in a rainstorm. Ten patients had a preceding "cold," which in that climate may be called facetiously a "warm." All responded promptly to therapy with penicillin.

Reports of studies on pneumonia usually emanate from hospitals. Shaw and Fry made investigation on patients kept at home. Eighty acute infections of the lungs (52%) were classified as pneumonia, 28% as influenza with pulmonary involvement, and 20% as bronchitis. Pneumococci, H. influenzae, and staphylococci were regarded as causes in 17%. A and B virus of influenza, psittacosis, and viral pneumonia were proved to be present or suspected in 19%. In the majority of cases the cause was unknown.[144]

Unsuspected, fulminating, fatal pneumonia occurred in two patients under treatment with cortisone and corticotropin for rheumatic disease. The symptoms were suppressed by the hormones.[145]

The mortality rate of patients with pneumococcal meningitis who received adequate sulfonamide-penicillin therapy was 28% of 43 attacks. If all cases were considered the rate was 45% of 84 attacks. Prognosis is worse after the age of 50. Infection of the middle ear was the chief cause; pneumonia seldom was present, and often no source was evident.[146]

Subacute Bacterial Endocarditis. — A short course of therapy with 600,000 units (360 mg.) of penicillin every six hours for 10 days, 0.5 gm. of streptomycin every six hours for 5 days, and half the amount for five days more, was satisfactory.[147] Of 19 patients who had been treated with antimicrobics, only 4 led normal lives later. After three to seven years, 10 were living, and of these, 4 had cardiac insufficiency, 1 was paralyzed, and 1 had mitral stenosis.[148]

Gonorrhea.—Despite effective available antimicrobic therapeusis, gonorrhea has not been controlled. An increase in the number of cases is reported. From experimental studies, it appears that all infections do not cause a purulent urethral exudate and discomfort. In that event, male victims may not be aware of an infection and may not seek medical aid. They are a source of infection for others. Macroscopic and microscopic examination of the urinary sediment provides a simple method of diagnosis and for "case finding." Presumptive diagnosis is possible in 75% of patients.[149]

Rheumatic Fever

Prevention. — Viral pharyngitis occurs more often than hemolytic streptococcal sore throat except during small epidemics of the latter. In one series of 1400 patients with acute pharyngitis, no hemolytic streptococci were found in 29%, and in 38% the leucocyte count was normal. These may be classified as viral pharyngitis for which antimicrobic therapy is unnecessary. Oxytetracyline given to 500 patients with streptococcal sore throat reduced the carrier

rate 55%. The antistreptolysin response was almost 50% less in treated patients than in untreated ones. Pharyngitis recurred more often in the treated group, but the attack rate of subsequent rheumatic fever was less.[150] Sulfadiazine does not eradicate streptococci or prevent rheumatic fever.[151] Penicillin is superior to other antimicrobics and to sulfadiazine.

The American Heart Association published revised recommendations for the prevention and treatment of hemolytic streptococcal infections to forestall initial attacks and recurrences of rheumatic fever. Details of the methods were described. Prophylaxis, it is said, should be continued for life, even during the summer, in persons who have had rheumatic fever. Penicillin is the agent of choice unless the person is hypersensitive to it.‡ Finland favors the continuous use of penicillin in this respect, but he believes the matter should be reviewed critically from time to time. It should be determined whether the procedure leads to the appearance of penicillin-resistant flora or to other untoward effects. It may be better to give penicillin promptly for streptococcal infections as they arise or after known exposure to streptococcal infection.[154] In answer, one relevant paper has appeared. According to Miller and Massell, long-term therapy with penicillin given orally thus far has caused no major changes in the flora of the throat that may predispose persons to serious superinfection.[155]

At a conference, doubt was expressed that the incidence of rheumatic fever has declined as much as statistical evidence shows. The decline may be more apparent than real and may be the result of improved environmental conditions rather than a change in the organic process.[153] A study was made of genetic relatives of rheumatic fever patients. Of 121 children from susceptible families, 40 had rheumatic fever, while among 525 children from nonsusceptible families, only 3 had the disease. The observations reemphasize the importance of heredity in rheumatic fever as a simple recessive trait.[156]

A discussion of the differential diagnosis of rheumatic fever in office practice gives practical information how to evaluate murmurs, changes in sedimentation rate, low-grade fever, tachycardia, and electrocardiographic tracings to decide whether or not the disease is present.[157]

The pathologic changes in the lung observed in 35 patients with rheumatic pneumonia are unspecific. They are similar to those of chemical irritation, polyarteritis, uremia, and other conditions. The lesion seldom is recognized clinically.[158]

Therapy.—In collaborative study by British and American physicians, neither cortisone, corticotropin, nor acetylsalicylic acid brought about uniform termination of rheumatic fever. Hormones caused rapid clinical improvement but a greater tendency to recurrence. At the end of a year, there was no significant difference in residual cardiac injury after treatment with the three agents.[159] Massell's experience, however, favors the use of hormonal therapy. When given early in the disease in larger doses for a longer time, better results were obtained despite the risk of side-effects.[160] According to Bunim[161] and Boland,[162] new synthetic steroids, hydrocortisone, prednisolone (Meticortelone), and prednisone (Meticorten) were more effective in smaller doses as anti-inflammatory drugs and gave different side-effects than cortisone and corticotropin. Clough, in reviewing the matter, decided that the currently available observations are not highly encouraging.[163] Report on further study is awaited with interest.

Valvotomy.—Early enthusiasm for the success of valvotomy is waning. Objective changes after operation often are not striking.§ Deaths occur from cardiac failure, from the postcommissurotomy syndrome, and from rheumatic restenosis.[166] Bacterial endocarditis with antimicrobic-resistant

‡ References 152 and 153.

§ References 164 and 165.

staphylococci and other bacteria also occurs.[167] In one series of 45 patients, streptococcal valvular infection followed operation in 12, or 27%.[168] These untoward effects may ensue even in patients most likely to be aided by valvotomy.

Experimental Studies.—Improved immunochemical methods were used to detect antecedent infection with Group A streptococci in 580 patients. In the first two months after the onset of rheumatic fever, high initial titers of either antistreptolysin O, antistreptokinase, or antihyaluronidase were in the serums of almost all patients. The rate of fall in titer had no relation to the subsequent course of the disease. Relapse, unprovoked by streptococcal infection, may occur within two months, but afterward, recurrence of rheumatic fever was associated with immunologic evidence of a new streptococcal infection.[169]

It is unlikely that all cases of chorea minor are rheumatic in origin. Tests, like those just mentioned, made within a month after chorea began gave positive results in 73% of patients and later, in only 45%. Perhaps the usually delayed appearance of chorea allows the titers of the serologic reactions to diminish or disappear.[170]

By special methods, Morse and his coworkers caused pharyngeal infection and bacteremia with a Group A streptococci in rabbits. A form of carditis not due to direct bacterial infection usually followed. If such changes are analogous to those occurring in patients with rheumatic fever, their appearance within 24 hours after infection suggests the operation of a nonimmunogenic mechanism. The possibility is a challenge to the theory of an antigen-antibody reaction as the chief cause of rheumatic lesions.[171] Perhaps a role is played by a crystalline proteolytic enzyme made by strains of Group A streptococci which acts as a powerful cardiac poison.[168] In other studies, streptococci persisted in the tissues without bacteremia for 104 days in inoculated rabbits. This seemed to support a view that the development of rheumatic fever depended more on the persistence of streptococci than on an antigen-antibody reaction. Cocci appeared in the blood after cortisone was injected.[172] Obviously, the etiology of rheumatic fever still is unsettled.

Rheumatoid Arthritis.—Dresner reviewed current theories of the cause of rheumatoid arthritis. The disease is not localized in joints, but is a generalized one of connective tissue. The nature of the fibrinoid changes is unknown. A direct bacterial or viral cause is unlikely, nor does the concept of disorder of adaptation seem to be important.[173]

Bacillary Infections

Tuberculosis.—According to a report by a life insurance company, the death rate from tuberculosis fell to its lowest in 1955—8 per 100,000.[1] Among children in one hospital, the death rate before the advent of antimicrobic therapy was 21.5%; by 1953, it was 1.5%.[174] Similar favorable report comes from England, but with a mortality at present of 10%. The important causes of death are miliary dissemination and meningitis.[175] Since the morbidity rate has not kept pace with the spectacular decline in mortality, it is obvious that preventive measures must be improved.

According to Myers, the tuberculin test is more accurate than mass roentgenographic survey to discover tuberculosis (and cheaper too). In most instances, disease can be detected in its earliest stages.[176] Eloesser outlined a plan for the control of tuberculosis in countries of limited means.[177]

Prevention.—Experiments with isoniazid in animals suggested its possible use as a prophylactic agent against tuberculosis. Whole populations, it is said, can be treated for as little as a cent a day per person.[178] It is doubtful, however, whether chemoprophylaxis is desirable except under special circumstances. The danger of masked infection, the development of drug-resistant strains, untoward reactions, subsequent infection, and interference with development of natural immunity must be considered.

BCG Vaccination.—Enthusiasm for mass vaccination was dampened in Scandinavian

countries, where in places it is compulsory. The matter was the subject of debate.[179] Gedde-Dahl, of Norway, and Wallgren,[180] of Sweden, once an advocate of the procedure, now have views in harmony with many American authorities. A decline of tuberculosis in countries with low morbidity can hardly be brought about by vaccination. Only a small number of persons vaccinated are exposed to infection. The procedure should be reserved for persons exposed to tuberculosis in the home and for tuberculin-negative nurses, attendants, and medical students in contact with tuberculous patients. In regions of high morbidity, and where no other measures are feasible, all tuberculin-negative children should be vaccinated as early in life as possible.

One investigator writes that previous objection to the instability and variability of BCG vaccine has been overcome by the use of a "freeze dried" product.[181] In other studies, calcification of the axillary lymph nodes draining the site of vaccination was demonstrated, occasionally as early as two months, in 20% of 34 white children.[182] A new kind of vaccine made of disintegrated tubercle bacilli by Youmans gave protection to experimentally infected mice.[183] The vaccine probably is free of the danger of causing infection.

Therapy.—So many reports advocate this or that combination of streptomycin, aminosalicylic acid, and isoniazid for treatment that further review may be postponed until agreement is reached. Muschenheim, for one, calls attention to the current diversity of opinion. Various forms or stages of tuberculosis require different therapeutic measures. He has had good results from isoniazid alone for minimal lesions and in some cases of moderate or far-advanced disease. Isoniazid is essential in meningeal and miliary tuberculosis.[184] Isoniazid therapy alone given over a year was successful in chronic disease.[185]

To aid physicians in selecting the desirable combination of drugs in therapy, Sweany recommends the following: streptomycin and isoniazid for critical cases, streptomycin and aminosalicylic acid for ordinary ones, and isoniazid and aminosalicylic acid when resistance to streptomycin develops. The use of the three drugs together seems to have no advantage.[186] An evaluation of present-day therapy was made by Amberson.[187]

Of six patients with tuberculous meningitis treated with streptomycin and isoniazid, one died and three have residual derangements. Of six given cortisone in addition, all but one recovered completely. Cortisone presumably suppresses the cellular reaction and lessens the danger of later fibrosis and obstruction.[188] In most cases of tuberculous meningitis the amount of sugar and chloride in the spinal fluid were low, but in a significant number, one or the other was normal in amount initially and remained so. Of the two, measurement of the chloride is the more reliable for diagnosis. Neither provides an index for prognosis.[189]

Streptomycin failed to eliminate tubercle bacilli from the urine in 25 of 90 patients with renal infection.[190] In Latimer's experience, the incidence of renal tuberculosis has not declined since the advent of streptomycin.[191]

Drug Resistance.—Tubercle bacilli somewhat resistant to streptomycin or isoniazid were encountered in 11% of 385 previously untreated patients. Only six strains were significantly resistant to streptomycin and nine to isoniazid.[192] In another report, 10 instances of infection with drug-resistant bacilli were found among 600 cases.[193] Among 563 samples of sputum collected from the streets of Ankara, tubercle bacilli were present in 27, and of these, 11 were drug resistant.[194] The threat of an increasing number of new infections with resistant strains does not appear to be ominous at present. There is controversy as to whether tubercle bacilli rendered resistant to isoniazid behave differently from those resistant to streptomycin. Suggestion was made that isoniazid-resistant mutants are "attenuated," but there is no evidence that this occurs in treated patients.[195]

Other Studies.—In a special issue of *The American Review of Tuberculosis and Pulmonary Diseases,* in March, 1955, Medlar summarized his extensive studies from 1927 to 1952 on the behavior of tuberculous pulmonary lesions.

Malnutrition is considered by Dubos as a factor in reducing resistance to tuberculosis perhaps by reducing the store of glycogen. Susceptibility of mice to infection was increased by deprivation of food for 30 hours afterward, but not by undernutrition from a constant low intake of food. Resistance was reduced by a diet low in protein and rich in carbohydrate, unless the carbohydrate were replaced by fat. Dinitrophenol and thyroxin shortened the survival time and made it possible to cause infection with BCG. Depletion of glycogen or reduction of glycolytic activity and an increase of certain acids and ketones seems to reduce the resistance of mice to tuberculosis.[196]

Confusion of tuberculosis with sarcoidosis persists. Of seven siblings, one had sarcoidosis and three had sarcoid-like disease. These three were said to have atypical tuberculosis on the basis of histologic changes resembling tuberculosis in biopsy specimens and the familial incidence. No tubercle bacilli were seen. The authors felt that tuberculosis may be one of the causes of sarcoidosis, or some other infection may have been present.[197] One wonders if histoplasmosis were ruled out. Tubercles were present in the liver at biopsy in 16 of 25 tuberculous patients. Except for the presence of bacilli, the lesions were indistinguishable from those of sarcoidosis, and they were present in the same percentage of cases.[198]

Hepatic biopsy revealed changes in the liver in 49 of 59 patients with chronic tuberculosis in India. Presumably they were caused by toxicity and may end in cirrhosis. Similar changes were not found in 34 undernourished, nontuberculous patients.[199]

By means of a transparent rabbit-ear chamber, it was possible to observe the evolution of a tubercle from its earliest stage after about 10 days to its full development in the second week.[200] Chronic tuberculosis established experimentally in rabbits provides a means to study the effect of hormonal therapy on the disease.[201]

Acid-fast bacilli, not Mycobacterium tuberculosis, were isolated from exudates and pulmonary tissue of patients with known or suspected tuberculosis. Some were virulent for mice, others were not and had no association with the patient's disease. Their significance is unknown.[202] In one sanatorium acid-fast bacilli not pathogenic for guinea pigs were excreted by tuberculous patients, 18 of whom had been treated.[203] The matter is of increasing importance in respect to the alterations of M. tuberculosis induced by modern therapy.

Typhoid.—The incidence of typhoid as reported in 1954 was 1.4 per 100,000. In New Mexico, Arkansas, Kentucky, and Louisiana, the rate exceeded 4.5 per 100,000.[204] Benavides, in Mexico, treated 15 patients with synnematin B. The results were said to be as good as those brought about by chloramphenicol, and typhoid bacilli were absent in the stool afterward.[205] If the carrier state actually is prevented, synnematin is the first agent to do so. The results need confirmation. Pang and I used chloramphenicol in the treatment of 52 Indonesian patients with paratyphoid A. As in typhoid, fever declined to normal after about five days. The disease was shortened from an average of 24 days in untreated patients to 16 days in treated ones. The relapse rate of 18% was unaltered, and the mortality-rate was the same, about 2%, regardless of treatment. In several severely sick patients a short course of cortisone therapy caused striking improvement. In one it had no effect.[206]

In a patient aged 70, typhoid infection of the hip developed 58 years after an attack of typhoid.[207]

Other Salmonella.—Watermelons injected with water to increase their weight caused food poisoning in 17 persons. The water apparently was polluted, and the melons contained Salmonella sp. (Type Miami). A

similar but smaller outbreak occurred in Rochester, Minn. Melons may be infected by slicing with dirty knives.[208] In one study, 23% of 217 samples of fresh pork sausage and 12% of smoked sausage contained Salmonella. Of sausage meat derived from local abattoirs, 57% had Salmonella in it, in contrast with 7.5% from national ones. Hogs are infected by contact with carrier animals when crowded in pens.|| An outbreak of 29 cases of salmonellosis in infants and children in Minnesota was traced to contact with infected chicks purchased at Easter time.[211] Ducklings were the source of similar disease among children in Binghamton, N. Y. An unexpected source of Salmonella was discovered in dried yeast given therapeutically to five patients. Three kinds of Salmonella were present.[212]

Shigellosis.—Studies by Higgins and his associates show that neither specific vaccine nor prophylactic administration of sulfadiazine, dihydrostreptomycin, or oxytetracyline serve to prevent bacillary dysentery in an endemic region of shigellosis.[213] Two Egyptians point out the importance of recognizing chronic bacillary dysentery when there is no dysentery or diarrhea. Constipation, abdominal pain, and "dyspepsia" may be the only symptoms.[214] Similar circumstances pertain to amebic dysentery and amebiasis. "Large race" Endamoeba histolylica cause disease more often than the "small race" forms, although healthy carriers may harbor both.[215]

In a symposium on diarrheal diseases published in the July issue of *The American Journal of Tropical Medicine and Hygiene,* Wegman casts doubt on the importance of paracolon bacteria, Proteus, Pseudomonas, and certain supposedly pathogenic colon bacilli as causes of epidemics of diarrhea. Gordon reviewed evidence in favor of filtrable agents as causes of large epidemics of mild diarrheal disease (viral dysentery).

Brucellosis.—Over 2000 cases of brucellosis in a three-year period were studied in Iowa. The incidence was greatest in the summer. Among farmers, most cases occurred during the two months after the farrowing of sows, probably as a result of close contact. Intradermal skin tests with specific antigen were more effective than the agglutinin tests for detecting inapparent, latent, or chronic infection.[216]

Tetanus.—Tetanus was observed in 22 patients in one hospital in a 20-month period. Twelve were diacetyl-morphine (heroin) addicts, and all died except one who was treated with cortisone in addition to the usual therapy. Among nonaddicts 40% died. Prophylactic injection of 10,000 units of antitoxin was an important factor in recovery.[217] Chlorpromazine hydrochloride, in combination with phenobarbital sodium, satisfactorily controlled tetanic spasms for 8 to 12 hours.[218]

In experiments on animals, oxytetracyline and penicillin seemed to be bactericidal for the vegetative forms of Clostridium tetani and eliminated tetanus infection. If this be the case, it may be desirable to give both antitoxin and an antimicrobic for prophylaxis against tetanus in man. The antimicrobic should be injected within 24 or 48 hours after infection, during the period of bacterial multiplication and liberation of toxin.[219]

In two papers in *The Lancet* of Feb. 19, 1955, the isolation of Clostridium welchii, Type D, was reported. The bacilli apparently secrete a toxin. The subject was reviewed editorially in the same issue.

Leprosy.—To counter the optimistic report of Lowe about the value of sulfone therapy in leprosy mentioned in last year's review, Jopling states that nearly all of his patients so treated had repeated attacks of fever, erythema nodosum, and other symptoms.[220] Evidently the treatment of leprosy needs improvement.

Among 50 necropsies, tuberculoid lesions were found in only 2. Amyloid was found in 23. Mycobacterium leprae were seen in the tissues of 34 subjects, including those who had received sulfone therapy for at least two years. The average duration of

|| References 209 and 210.

life after the onset of disease was 20 years, and the average age at death was 59.[221]

Miscellaneous.—A newly recognized bacillus, Pasteurella novicida sp. nov., isolated from water in Utah, closely resembles P. tularensis and is virulent for rodents.[222] Strains of P. pestis were classified into three antigenic groups.[223] Antipertussis vaccine occasionally causes fatal neurologic disturbance in infants. However, electroencephalographic tracings from 33 vaccinated children showed changes in only 2.[224] Skin tests and stained smear preparations from exudates were not wholly reliable for the diagnosis of chancroid. Chlortetracyline and oxytetracycline are effective in therapy, but sulfadiazine or streptomycin are preferred because they do not mask syphilis if it is present.[225] Alston collected reports on 280 cases of infection with Bacillus necrophorus. Of his own 12 patients, 7 died. The bacillus causes infection in various sites, pyemia, and abscesses.[226] Garrod found some strains to be sensitive to penicillin, others to oxytetracyline.[227] Guinea pigs inoculated with streptomycin-resistant Vibrio comma were infected when the normal intestinal flora was suppressed by streptomycin.[228] One wonders if the same circumstance holds for man. In my experience in Chungking, experimental therapy with streptomycin had no harmful or beneficial effect on patients. Immunization of guinea pigs with dead vibrios gave effective protection against infection.[228]

Fungal Infections

Histoplasmosis.—There is no apparent danger of the direct transmission of histoplasmosis from infected animals to man. Infected animals, however, provide an index of the geographic distribution of histoplasmosis and serve as hosts for the propagation of the fungus. During an eight-year study, Histoplasma capsulatum was recovered from dogs, cats, mice, rats opossums, skunks, foxes, and woodchucks. Animals usually were healthy carriers.[229] One wonders if birds and barnyard fowl are implicated.

Two epidemics were described. In one, five persons were infected by inhaling histoplasma-bearing dust in a chicken coop. Dogs, cats, chickens, and cows on the premises gave evidence of infection, and the fungus was isolated from dogs and a cat.[230] In the other, seven persons exposed to the dust of dried pigeon manure developed illness diagnosed as psittacosis, in 1947. In 1952, after roentgenograms were made, restudy indicated that the disease was histoplasmosis.[231] Two probable cases and a proved case of histoplasmosis occurred in persons exposed to infection in a laboratory where work on the disease was in progress.[232]

The source and cause of an unidentified infection of the respiratory tract similar to "cave disease" in the United States was discovered in Peru. H. capsulatum was recovered from the soil in a cave inhabited by a variety of birds and animals and often entered by tourists and natives. The histoplasmin skin test gave positive results in 43% of residents in the vicinity.[233] A review of knowledge of histoplasmosis was published. An estimated 20,000,000 to 30,000,000 people in the United States have histoplasmosis in varying degrees of severity, mostly mild and unrecognized.[234]

Knowledge of pulmonary histoplasmosis was reviewed by Schwartz.[235] Among 105 patients who died from various causes, healed primary complexes with stainable fungi, presumably H. capsulatum, were found in 67%. The lesions resembled those of tuberculosis.[236] The high percentage reported makes one wonder if H. capsulatum can be identified on morphologic grounds alone. Puckett reported on 67 patients with pulmonary histoplasmosis treated surgically for the removal of pulmonary tissue or lymph nodes. Tuberculoma or coin lesion had been diagnosed in many, and 31 had no symptoms.[237]

In one hospital service, of 300 patients, 24% yielded serologic evidence of either histoplasmosis, coccidioidomycosis, or blastomycosis.[238] At a tuberculosis sanitarium, 2.2% of inmates considered to be tuber-

culous actually had histoplasmosis, and 5.3% gave a positive reaction to the skin test or serologically with histoplasmic antigen.[239] The central nervous system may be involved during histoplasmosis, as it is in tuberculosis. Lesions were found in the brain and/or meninges in 6 of 11 cases.[240]

A series of papers in a book on the therapy of fungal diseases cite disappointing results in the treatment of histoplasmosis and coccidioidomycosis. Nystatin (Mycostatin) had some favorable influence in animals inoculated with coccidioides immitis, and sulfonamide drugs retarded infection with H. capsulatum.[241]

Coccidioidomycosis.—Wild rodents apparently are not an important reservoir of coccidioidomycosis. More than 1000 rodents trapped in endemic areas were examined, but only eight, 0.7%, yielded evidence of infection.[242] C. immitis was recovered from 7% of 500 samples of soil in the San Joaquin valley. The incidence was 13% in samples collected from burrow walls of animals.[243] Mycelial forms of C. immitis were demonstrated for the first time in sputum, in pulmonary cavities, and in granulomatous areas. Despite the presence of mycelia, there is no evidence of contagiousness of coccidioidomycosis.[244]

In nondisseminated coccidioidomycosis, the skin test becomes positive first and specific serologic reactions follow. The precipitin test is positive in the third week, and complement-fixing antibodies appear more slowly but persist longer. In the disseminated form, the complement-fixation reaction was positive in most cases, and the titer reflected the severity of the disease. A falling titer usually indicates a better prognosis. Fixation of complement by spinal fluid occurs when meningitis is present.[245]

Coccidioidomycosis may be mistaken for neoplastic disease, osteomyelitis, and other diseases.[246] Indications for surgical procedures in pulmonary coccidioidomycosis are giant cavity, secondarily infected cavity, checkvalve cavity, ruptured cavity, coccidioma, and continued hemoptysis. Cavities seldom close after six months. Operation was successful in all but 3 of 100 patients.[247]

Pedal Dermatomycosis ("Athlete's Foot").—Baer and his associates add more evidence, if more is needed, to lay the myth of exogenous infection as the source of pedal dermatophytosis. Infection when it does occur most likely results from lowered local resistance and the invasion of ever-present fungi.[248] Experimental attempts failed to incite infection in 68 volunteers. Danger of contagion from bathmats, floors, socks, and so forth is minimal.[249] A curious and minor point is the use of the term human volunteers by these authors and in several other papers covered in this review. What other kind of volunteer is there?

Three cases of disseminated candidiasis were described in patients who had had extensive antibiotic therapy and were in generally poor condition. Two of them died, one recovered but developed chronic pyuria caused by Candida.[250] Another patient developed moniliasis and aspergillosis after therapy with corticotropin.[251]

Protozoal Infections

Amebiasis.—In a farming area in Nebraska where imported laborers are heavily infected with E. histolytica, the incidence of intestinal parasitism in the local population is no greater than the national average. Evidently, ordinary measures of sanitation suffice to limit the spread of infection. Infection seems to be more easily transmitted by close personal contact than by fecal pollution of water and food.[252] In modern communities the same holds true for viral hepatitis, viral and bacillary dysentery, and typhoid. According to Mackie, amebiasis, like poliomyelitis, is a familial disease. Infections with E. histolytica were 30 times more frequent among families containing infected school children than in families with uninfected children.[253]

There is controversy about amebic hepatitis, said by some observers to be present at times during amebic dysentery. Nelson and his co-workers found evidence of hepatic dysfunction in 29 of 371 patients

with amebiasis. Twelve tests and signs were used to establish diagnoses of probable hepatitis. Positive specific diagnosis can be made only if amebas are demonstrated in hepatic lesions. Most of the 29 patients were aided by therapy with erythromycin. In nine who were resistant to therapy, chloroquine benefitted six.[254] Kean, who examined many cases at necropsy and 50 biopsy specimens, was unable to demonstrate specific diffuse hepatic lesions. Amebic hepatitis, he believes, cannot be regarded as an entity. The clinical syndrome may arise from nonspecific effects of intestinal ulceration or from other causes.[255]

The matter of ameboma is less confused. According to Radke, tumor-like thickening of the intestines, now called ameboma and regarded as a new observation, was described in 1828. He analyzed 119 reports of cases. The mortality rate was 40%. Malignancy often is suspected. Combined quinacrine-carbarsone therapy is recommended. The use of emetine, he writes, should be abandoned.[256]

Good results in the treatment of acute amebiasis are reported after treatment with erythromycin. Chronic disease was treated with an initial dose of 800 mg. followed by 300 mg. every six hours for five days.[257] Anderson combines fumagillin with erythromycin for hepatic amebiasis.[258] Question arises as to whether antibiotics act on amebas or on the bacteria which may play an etiologic role, as suggested by studies mentioned in the next paragraph.

Evidence of bacterial participation in amebiasis was obtained by study of "germ-free" animals raised and kept in a special environment. No lesions developed when germless guinea pigs were inoculated with amebas. When 37 normal, germ-laden animals were inoculated as controls, 34 developed ulcerative amebiasis and 3 harbored amebas for 21 days. Another group of germ-free guinea pigs was fed a variety of enteric bacilli before inoculation with amebas, and all developed amebic disease.[259]

Malaria.—In experiments on volunteers infected with the Chesson strain of virax malaria, quinine, chloroquine, quinacrine, and pamaquine were ineffective prophylactically. When primaquine was given in weekly doses of 30 mg. for 15 weeks, three of five volunteers had relapse after the last dose. When 30 mg. was given twice a week, relapse occurred in 2 of 12. The latter regimen or primaquine plus chloroquine once a week is recommended.[260] It remains to be seen whether the same good results will pertain in the prevention of infection with other strains of plasmodiums.

Malaria recurred in a 56-year-old man 36 years after the original infection.[261]

Trichomonal Infection.—Trichomonas vaginalis infection in men is important in respect to causing infection and reinfection in women during coitis. Coutts and his coworkers describe acute, chronic, and latent infections in men. Systemic involvement may occur.[262]

Toxoplasmosis.—The Feldman-Sabin dye test gave positive reactions in 68% of Tahitians and 4% of Navaho Amerinds. No Eskimos reacted positively. The test was positive in 30% of the dogs owned by the Navahos.[263] Mention was made in last year's review of doubt cast by Awad on the specificity of the test and on the validity of epidemiologic inferences based on its use. That the test is a specific one was reaffirmed by Sabin in discussion at the November meeting of the American Society of Tropical Medicine.

The seventh case of toxoplasmosis accidentally acquired in the laboratory was described. A finger was pricked while handling a culture of the microbe.[264]

Leishmaniasis.—Visceral leishmaniasis (Leishmania donovani) was discovered in a dog in Florida. The animal probably had been infected in Greece. There is a possible danger of planting the disease in Florida, one of the few places in the United States where there are Phlebotomus flies.[265] An unusual epidemic of kala-azar involved about 300 persons in Africa in an 18-month period. Seventy per cent were male, and fifty-seven per cent of cases occurred during the ages of 4 and 18 years. Sand flies

were suspected as vectors. Victims who developed post-kala-azar dermal lesions may be sources of infection.[266] Three persons suspected of having leprosy in Panama actually had mucocutaneous leishmaniasis (espundia). In two there was evidence of hitherto undescribed systemic involvement.[267]

Trypanosomiasis.—C. F. Craig predicted the discovery of American trypanosomiasis (Chagas' disease) in the Southern United States years ago, and Packchanian demonstrated specific immune bodies in the blood of 40 Texans.¶ A case was found recently in an infant suspected of having leukemia because of lymphocytosis. Trypanosoma cruzi were in the blood, and Triatoma bugs were suspected as the source of infection. Tetracycline therapy seemed to be curative, but trypanosomes persisted in the blood.[268]

Miscellaneous Subjects

Rickettsioses.—The transmission of Rocky Mountain spotted fever to man and its perpetuation in nature was thought to depend on infected ticks.[269] However, the Rickettsia were found for the first time in naturally infected meadow mice by Gould.[270] The incidence of the disease ranks with or exceeds that of typhus in Southeastern United States. Contrary to early belief, the mortality rate is the same for the Eastern and Western varieties.[269] The originally reported high death rate of 90% in the Bitterroot Valley of Montana has not been explained except to surmize that mild cases were undiagnosed and not included in the statistics. Treatment with appropriate antimicrobic drugs masks the disease and obscures clinical and laboratory diagnosis. In another study, viable Rickettsia were found in lymphoid tissue of a patient a year after recovery.[271] Demonstration of the persistence of Rickettsia further supports Zinsser's concept regarding the identity of Brill's disease and epidemic typhus.

In Chicago, antibody against typhus was present in the serum of 22% of persons between the ages of 50 and 76 who were born in Eastern Europe. No antibody was found in native Americans. Typhus should not be diagnosed serologically unless the antibody titer rises.[272]

Sarcoidosis.—Further study was made to determine why sarcoidosis is more prevalent among people who live in the Southeastern United States than elsewhere. Although Negroes predominated, the geographic preponderance of cases could not be ascribed to racial factors alone. A significant correlation pertained to residence in rural regions where the soil is podzolic. Whether sarcoidosis is a manifestation of a single causative microbe agent found in such soil or is due to changes inherent in persons living in these areas is unknown.[273]

Syphilis.—The treponemal immobilization (TPI) test gave satisfactory recheck results in patients. Among 733 samples of serum which gave a positive reaction to the standard tests for syphilis, the TPI test gave positive results in 370, negative ones in 338, and doubtful ones in 25.[274] English observers conclude that the test has no advantages over the older ones in the diagnosis of early symptomatic syphilis, but it is of value in the diagnosis or exclusion of suspected latent disease,[275] and, one may add, in the clarification of falsely positive reactions.

Relapsing Fever.—Eleven fatal cases of louse-borne relapsing fever were studied in Korea. Characteristic recurrent episodes of fever as described in textbooks were absent. Follicular splenic abscesses, interstitial myocarditis, intracranial hemorrhage, and hepatitis were prominent features. Six patients had coexistent infection with Salmonella or Shigella. Histologic sections from 20 fatal cases previously diagnosed as salmonellosis or shigellosis were then reexamined. Borrelia were present in the tissues of four.[276] Salmonellosis also may occur during viral hepatitis. Evidently enteric bacilli may become invasive when resistance is lowered by various causes.

¶ Packchanian, A.: Personal communication to the author.

Trichinosis.—Over 10% of adults have been mildly infected with Trichinas. Small numbers of ingested live Trichinas are said to evoke a degree of immunity. If this is so, according to Magath and Thompson, the trichinacidal irradiation of pork would eliminate this stimulant to immunity and may render people susceptible to a severe infection.[277]

Appendicitis.—Editorial comment dwells on the figment of chronic appendicitis. Pathologists may abet a clinical diagnosis by reporting minor changes in an appendix which were the result of previous mild disturbance or from trauma at operation. No lesion conforms with the concept of persistent low-grade appendiceal disease apart from tuberculosis, actinomycosis, and a few other rare conditions.[278]

Trachoma.—Some investigators suspect a Miyagawanella of the psittacosis group as the cause of trachoma. Others favor a virus or the agent described by Prowazek and Halberstaedter in 1907. Since sulfonamide drugs, oxytetracycline, and chlortetracycline are said to be effective in therapy, it is probable either that the cause is not a virus or that therapy eliminates secondary bacterial infection and allows the tissue to cope with a virus. Trachoma occurs chiefly in regions of poor sanitation and poverty. Exposure to heat, sunshine, wind, and dust favor infection. Trachoma is endemic in Missouri, Arkansas, and southern Illinois.[279]

Peridontitis.—A mixture of gingival bacteria was thought to cause lytic changes and lead to inflammation of the gums. Oral bacteria were cultivated from areas of chronic marginal gingivitis in 13 of 19 patients, but from only 3 of 21 persons whose gums were healthy.[280] Question remains whether the microbes are pathogenic or thrive as saprophytes in tissue injured otherwise. For example, after tonsillectomy or extraction of teeth, the site of operation may swarm with microbes of oral origin.

Isosporosis.—Of the 27 cases of infection with Coccidium isospora reported on in the United States, 18 probably were not indigenous, and some of the rest may have been acquired by contact with persons infected elsewhere. Three persons whose stools contained the Coccidium were observed in Georgia, two of whom may have been infected from dogs. One had diarrhea; the other two were symptomless.[281]

"New" Diseases.—By concidence, two diseases of similar nature were reported on from England and from Peru in the same issue of a journal. Except for prominent nervous symptoms, the signs, symptoms, and laboratory data resemble those of infectious mononucleosis or lymphocytosis.# Another disease thought to be viral in origin and related either to viral hepatitis or to infectious mononucleosis was observed in 43 patients in Colorado. The liver was enlarged and tender and its function was impaired, but without causing jaundice.[284] An epidemic, probably of viral origin, occurred in Japan among military personnel. It involved 50 patients who had epididymitis, often in association with pneumonia.[285]

During studies on malaria, a hitherto undescribed infection was encountered. Blood from an otherwise healthy donor regularly caused an influenza-like, febrile disease when injected into recipients. Blood samples from the donor were infectious over 13 months. Known infections were ruled out. A virus was suspected as the cause.[286] Besides the importance of being recognized as a "new" disease, it probably is another hazard to be considered when transfusing blood.

It is certain that still other infections currently unrecognized or nonexistant or confused with other diseases await discovery. As already mentioned in this review, new enteric and neurotropic viruses have been isolated. In recent experience in Lebanon and Indonesia, I observed a number of patients with febrile diseases of undetermined cause. Some resembled typhoid, others influenza or infectious mononucleosis. Luckily, investigators still have a field for research in this respect. Murray reviewed progress in bacteriologic knowl-

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edge and proposed new avenues for investigation.[287]

Adrenocortical Hormones.—Kilbourne demonstrated a suppression of antibody against influenza virus when cortisone was given continuously, but not after large doses were given only at the onset of infection. In mice with acquired immunity, small doses of cortisone insufficient to suppress antibody induced lesions and persistence of virus in the lungs.[288] The clinical use of adrenocortical hormones, according to Thomas, should not be extended beyond the conditions in which it can be predicted to be life-saving or to relieve intractable suffering.[289] After a comprehensive review of the matter, Kass and Finland pose this question: If inhibition of inflammation is generally harmful in diseases of known cause, is it not necessary to examine carefully the premise that such inhibition is beneficial in diseases of unknown cause?[291] Favorable results may ensue, however, after short periods of therapy, together with antimicrobics, in severe cases of lobar pneumonia,[290] typhoid, brucellosis, trichinosis, and tuberculous meningitis.

C-Reactive Protein Test.—The c-reactive protein test gives positive results in serum from patients within 14 to 26 hours after inflammation or destruction of tissue occurs. Reaction occurs during the acute phase of bacterial infections, rheumatic fever, and, less often, in viral infections and tuberculosis.[292] In another study positive results occurred most often during tonsillitis, scarlet fever, varicella, and mumps, but in only about 50% of tuberculous patients.[293] Reaction occurs also during myocardial infarction, widespread neoplastic disease, and occasionally in pregnancy,[294] but rarely in normal persons. Any degree of reaction may be considered to be abnormal.

Commensal Bacteria.—Hare and his colleagues studied 233 strains of anaerobic cocci obtained from various places in the body. Of these, 141 were regarded as commensals; the rest were isolated during various infections. Some of them were thought to be mildly pathogenic and of importance in lowering resistance to other infection.[295] The reverse more likely is the case, namely, infection by known agents or other disease lowers resistance sufficiently to permit anaerobic cocci, otherwise benign, to become invasive.

Over the years, the occasional recovery of diphtheroid bacilli and other bacteria from the blood and tissues of patients with malignant disease gave rise to speculation about their etiologic significance.[296] However, the results of a critical study suggested that such pleomorphic bacilli may have come from other sources. Contamination is implied. With use of special technique, no bacteria were found in the blood of patients with malignant disease.[297] Nevertheless, it is reasonable to expect bacteria ordinarily saprophytic to be invasive at times when resistance is lowered by chronic illness or other cause. Pasteurella multicida caused septicemia after a patient with hepatic cirrhosis was bitten by a cat.[298] Other examples were cited previously, as, salmonellosis during relapsing fever, bacterial invasion during therapy with antimicrobics and steroid hormones, and coccal septicemia after valvotomy. Transient bacteremia often occurs after dental surgery or catheterization.

Pleuropneumonia-like Organisms.—These microbes of uncertain etiologic status were isolated from two patients with puerperal sepsis, from one with pyosalpinx, and from one with empyema. No other cause but pleuropneumonia-like organisms (PPLO) could be found. Specific antibody developed in three, and in three recovery followed therapy with oxytetracycline to which PPLO was sensitive.[299]

Infections from Transfusion.—Brucellosis,[300] viral hepatitis, syphilis, measles, smallpox, malaria, typhoid, and kala-azar have been transmitted unwittingly by the transfusion of blood from donors who carry the respective causative agents. Attention was called also to the danger of fatal reactions after transfusing stored blood contaminated with bacteria able to grow in containers at temperatures between 4 and 8 C.[301] Toxins are formed by Pseudo-

monas, coliform bacteria, Achromobacter, and other Gram-negative bacilli which may escape detection by ordinary cultural methods.[302] Contamination of blood with bacteria which grow best at 37 C is less dangerous. Bacterial growth may be suppressed by adding minute amounts of a tetracycline drug to the blood. In other studies, psychrophilic bacteria which grow at temperature between 20 and 25 C contaminated 25% of animal serums, human blood, and other biologic products used for therapy. Tests for sterility should include incubation at low temperatures as well as the usual ones.[303]

Biologic Interference.—Interest and knowledge in the matter of biologic interference is increasing. Its occurrence leads to confusion in diagnosis and in experimental studies. In evaluating the epidemiology or effects of various induced infections, consideration must be given to the possible presence of other undetected and unrelated microbes in test animals or in explants of their tissues. Reference was made in this review to the problem in regard to yellow fever and dengue; poliomyelitis, Newcastle disease, and vaccinia; to viruses latent in simian renal tissue, and to chronic murine pneumonia. Increased resistance to reinfection by one pathogen may or may not be evidence of previous infection by the same or a closely related one. For example, guinea pigs exposed to Brucella suis and Coxiella burnetti developed brucellosis and Q fever, but were less affected than those inoculated with B. suis alone. Animals previously infected with B. suis resisted infection with C. burnetti. Interference is not explainable on the basis of demonstrable immunologic factors.[304]

In regard to genetic recombination in bacteria the following was written: ". . . in view of the ambiguity of haploid analysis, nondisjunctional types should be looked for. If the hypothesis of fractional fertilization is correct, interrupted matings should lead to 'diploids' that carry fragments of the Hfr genome. . . ." The problem seems to be as complex as the language which deals with it.[305]

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REFERENCES

1. Mortality Continues at Record Low in 1955, Statist. Bull. Metrop. Life Insur. Co. 37:1-5 (Jan.) 1956.

2. Welch, H.: The Growth, Development and Control of Antibiotics in the United States, Antibiotics & Chemother. (Supp. 1) 5:1-12 (April) 1955.

3. Chemotherapy of Bacterial Infections, Foreign Letters (England), J. A. M. A. 159:141-142 (Sept. 10) 1955.

4. Martin, W. J.; Nichols, D. R., and Heilman F. R.: Observations on Clinical Use of Phenoxymethyl Penicillin (Penicillin V), J. A. M. A. 160:928-931 (March 17) 1956.

5. Jones, W. F., Jr., and Finland, M.: Blood Levels from Orally Administered Penicillins G and V: Relation to Food Intake, New England J. Med. 253:754-761 (Nov. 3) 1955.

6. Quinn, E. L.; Colville, J. M.; Cox, F., Jr., and Truant, J.: Phenoxymethyl Penicillin (Penicillin V) Therapy of Subacute Bacterial Endocarditis, J. A. M. A. 160:931-936 (March 17) 1956.

7. The Pharmacopeia of the United States of America, Book Reviews, J. A. M. A. 159:977 (Oct. 29) 1955.

8. Allergy to Penicillin, Editorial, J. A. M. A. 160:778-779 (March 3) 1956.

9. Capsules, Medicine, Time 67:71 (March 5) 1956.

10. Berger, A. J., and Eisen, B.: Feasibility of Skin Testing for Penicillin Sensitivity: A Study of 1000 Cases, J. A. M. A. 159:191-193 (Sept. 17) 1955.

11. Darnell, J. E., Jr.; Pesch, B. B., and Glaser, R. J.: Effect of Penicillin on Group A Streptococci in Vivo in the Absence of Leucocytes, J. Clin. Invest. 34:1237-1241 (Aug.) 1955.

12. Eagle, H.: The Multiple Mechanisms of Penicillin Resistance, J. Bact. 68:610-616 (Nov.) 1954.

13. Finland, M.: Changing Patterns of Resistance of Certain Common Pathogenic Bacteria to Antimicrobial Agents, New England J. Med. 252:570-580 (April 7) 1955.

14. Dowling, H. F.; Lepper, M. H., and Jackson, G. G.: Clinical Significance of Antibiotic-Resistant Bacteria, J. A. M. A. 157:327-331 (Jan. 22) 1955.

15. Lepper, M. H.: Microbial Resistance to Antibiotics, Ann. Int. Med. 43:299-315 (Aug.) 1955.

16. Resistance of Micrococci (Staphylococci) to Antibiotics, Editorial, Ann. Int. Med. 42:954-959 (April) 1955.

17. Wise, R. I.; Cranny, C., and Spink, W. W.: Epidemiologic Studies on Antibiotic-Resistant Strains of Micrococcus Pyogenes, Am. J. Med. 20:176-184 (Feb.) 1956.

18. de Vries, J. A., and Pritchard, J. E.: The Increase in Serious Staphylococcal Infections as Shown by Post-Mortem Investigation, Canad. M. A. J. 73:827-828 (Nov. 15) 1955.

19. Restriction of Antibiotics? Leading Articles, Lancet 1:193 (Jan. 28) 1956.

20. Berntsen, C. A., Jr.: Unaltered Penicillin Susceptibility of Streptococci: Study of Alpha Hemolytic Streptococci Causing Endocarditis, 1944 to 1954, J. A. M. A. 157:331-333 (Jan. 22) 1955.

21. Finland, M.: Medical Progress: Emergence of Antibiotic-Resistant Bacteria, New England J. Med. 253:909-922 (Nov. 24), 969-979 (Dec. 1), and 1019-1028 (Dec. 8) 1955.

22. Weinstein, L.: Failure of Chemotherapy to Prevent the Bacterial Complications of Measles, New England J. Med. 253:679-683 (Oct. 20) 1955.

23. Watson, G. I.: Problems Involved in Prevention of Bacterial Complications of Measles, with Special Reference to Prophylactic Sulphadiazine, Brit. M. J. 1:5-10 (Jan. 1) 1955.

24. Meleney, F. L., and Johnson, B. A.: A Review of Systemic Bacitracin Therapy, U. S. Armed Forces M. J. 6:834-842 (June) 1955.

25. Altemeier, W. A., and others: Critical Re-evaluation of Antibiotic Therapy in Surgery, J. A. M. A. 157:305-309 (Jan. 22) 1955.

26. Sanford, J. P.; Favour, C. B., and Mao, F. H.: The Emergence of Antibiotic Resistant Gram-Negative Bacilli, J. Lab. & Clin. Med. 45:540-545 (April) 1955.

27. Potee, K. G.; Wright, S. S., and Finland, M.: In Vitro Susceptibility of Recently Isolated Strains of Proteus to 10 Antibiotics, J. Lab. & Clin. Med. 44:463-477 (Sept.) 1954.

28. Love, B. D., Jr., and Finland, M.: Susceptibility of Neisseria Gonorrhoeae to 11 Antibiotics and Sulfadiazine: Comparison of Susceptibility of Recently Isolated Strains with Results Obtained in Previous Years in the Same Laboratory, A. M. A. Arch. Int. Med. 95:66-73 (Jan.) 1955.

29. Susceptibility of Meningoccocci, Annotations, Lancet 1:90 (Jan. 8) 1955.

30. Love, B. D., Jr., and Finland, M.: In Vitro Susceptibility of Meningococci to 11 Antibiotics and Sulfadiazine, Am. J. M. Sc. 228:534-539 (Nov.) 1954.

31. Goldsmith, G. A.: Medical Progress: Current Status of the Clinical Use of Antibiotic-Vitamin Combinations, New England J. Med. 254:165-172 (Jan. 26) 1956.

32. Lynch, J. E.; English, A. R.; Bauck, H., and Deligianis, H.: Studies on the in Vitro Activity of Anisomycin, Antibiotics & Chemother. 4:844-848 (Aug.) 1954.

33. Groupé, V.; Pugh, L. H.; Levine, A. S., and Herrmann, E. C., Jr.: Suppression of Certain Viral Lesions by a Microbial Product, Xerosin, Lacking in Demonstrable Antiviral Properties and Produced by Achromobacter Xerosis, N. Sp., J. Bact. 68:10-18 (July) 1954.

34. Florey, H. W.: Antibiotic Products of a Versatile Fungus, Ann. Int. Med. 43:480-490 (Sept.) 1955.

35. Garrod, L. P., and Waterworth, P. M.: Behavior in Vitro of Some New Antistaphylococcal Antibiotics, Brit. Med. J. 2:61-65 (July 14) 1956.

36. Hudson, D. G.; Yoshihara, G. M., and Kirby, W. M. M.: Spiramycin: Clinical and Laboratory Studies, A. M. A. Arch. Int. Med. 97:57-61 (Jan.) 1956.

37. News Briefs, Science 122:915 (Nov. 11) 1955.

38. Oroshnik, W.; Vining, L. C.; Mebane, A. D., and Taber, W. A.: Polyene Antibiotics, Science 121:147-149 (Feb. 4) 1955.

39. Second Antibiotics Symposium, Pub. Health Rep. 70:495-496 (May) 1955.

40. Hilleman, M. R.; Werner, J. H., and Stewart, M. T.: Grouping and Occurrence of RI (Prototype RI-67) Viruses, Proc. Soc. Exper. Biol. & Med. 90:555-562 (Dec.) 1955.

41. Bell, J. A., and others: Adenoviruses: Group Name Proposed for New Respiratory Tract Viruses, Science 124:119 (July 20) 1956.

42. Hilleman, M. R.; Tousimis, A. J., and Werner, J. H.: Biophysical Characteristization of the RI (RI-67) Viruses, Proc. Soc. Exper. Biol. & Med. 89:587-593 (Aug.-Sept.) 1955.

43. Rowe, W. P.; Hartley, J. W., and Huebner, R. J. Additional Serotypes of the APC Virus Group, Proc. Soc. Exper. Biol. & Med. 91:260-262, (Feb.) 1956.

44. The Practice of Public Health, 1954: Respiratory System Viruses, Pub. Health Rep. 70:207-209 (Feb.) 1955.

45. Huebner, R. J., and others: Studies of the Adenoidal-Pharyngeal-Conjunctival Vaccines in Volunteers, J. A. M. A. 159:986-989 (Nov. 5) 1955.

45a. Bell, J. A., and others: Efficacy of Trivalent Adenovirus (APC) Vaccine in Naval Recruits, J. A. M. A. 161:1521-1525 (Aug. 18) 1956.

45b. Reimann, H. A.: Viral Pneumonias, Editorial, J. A. M. A. 161:1078-1079 (July 14) 1956.

46. Huebner, R. J.; Rowe, W. P.; Ward, T. G.; Parrott, R. H., and Bell, J. A.: Adenoidal-Pharyngeal-Conjunctival Agents: A Newly Recognized Group of Common Viruses of the Respiratory System, New England J. Med. 251:1077-1086 (Dec. 30) 1954.

47. Dingle, J. H., and others: Relationship of

Certain Characteristics of the New Respiratory Viruses to the Clinical and Epidemiological Behavior of Non-Bacterial Pharyngitis, Tr. A. Am. Physicians 68:73-77, 1955.

48. Harford, C. G.; Hamlin, A., and Parker, E.: Electron Microscopy of HeLa Cells Infected with ARD Virus, Tr. A. Am. Physicians 68:82-86, 1955.

49. Ormsby, H. L., and Aitchison, W. S.: The Role of the Swimming Pool in the Transmission of Pharyngeal-Conjunctival Fever, Canad. M. A. J. 73:864-866 (Dec. 1) 1955.

50. Parrott, R. H., and others: Outbreak of Febrile Pharyngitis and Conjunctivitis Associated with Type 3 Adenoidal-Pharyngeal-Conjunctival Virus Infection, New England J. Med. 251:1087-1090 (Dec. 30) 1954.

51. Bell, J. A., and others: Pharyngoconjunctival Fever: Epidemiological Studies of a Recently Recognized Disease Entity, J. A. M. A. 157:1083-1092 (March 26) 1955.

52. Hilleman, M. R.; Werner, J. H.; Dascomb, H. E., and Butler, R. L.: Epidemiologic Investigations with Respiratory Disease Virus RI-67, Am. J. Pub. Health 45:203-210 (Feb.) 1955.

53. Production of Pharyngoconjunctival Fever in Human Volunteers Inoculated with APC Viruses, Reports and Letters, Science 122:1086-1087 (Dec. 2) 1955.

54. New Type of APC Virus from Epidemic Keratoconjunctivitis, Reports and Letters, Science 122:1190-1191 (Dec. 16) 1955.

55. Kjellén, L.: Studies on an Unidentified Group of Cytopathogenic Agents, Arch. ges. Virusforsch. 6:45-59, 1955.

56. Ginsberg, H. S., and others: Etiologic Relationship of the RI-67 Agent to "Acute Respiratory Disease (ARD)," J. Clin. Invest. 34:820-831 (June) 1955.

57. Berge, T. O., and others: Etiology of Acute Respiratory Disease Among Service Personnel at Ford Ord, California, Fed. Proc. 14:457 (March) 1955.

58. Liu, C.; Eaton, M. D., and Heyl, J. T.: Studies on Primary Atypical Pneumonia, Bull. New York Acad. Med. 32:170-171 (Feb.) 1956.

59. Treatment of Virus Pneumonia, Foreign Letters (Sweden), J. A. M. A. 157:678 (Feb. 19) 1955.

60. Fitz, R. H.; Meiklejohn, G., and Baum, M. D.: Psittacosis in Colorado, Am. J. M. Sc. 229:252-261 (March) 1955.

61. Psittacosis (Ornithosis), Foreign Letters (Denmark), J. A. M. A. 159:1143 (Nov. 12) 1955.

62. Woolridge, R. L.; De Meio, J. L.; Whiteside, J. E., and Seal, J. R.: Epidemic Influenza B and C in Navy Recruits, 1953-1954: I. Antigenic Studies on Influenza Virus, Type B, Proc. Soc. Exper. Biol. & Med. 88:430-435 (March) 1955.

63. Andrews, B. E., and McDonald, J. C.: Influenza Virus C Infection in England, Brit. M. J. 2:992-994 (Oct. 22) 1955.

64. Grist, N. R.: Influenza A and C in Glasgow, 1954, Brit. M. J. 2:994-997 (Oct. 22) 1955.

65. Francis, T., Jr.: Current Status of the Control of Influenza, Ann. Int. Med. 43:534-538 (Sept.) 1955.

66. Jensen, K. E.; Minuse, E., and Ackermann, W. W.: Serologic Evidence of American Experience with Newborn Pneumonitis Virus (Type Sendai), J. Immunol. 75:71-77 (July) 1955.

67. Andrewes, C. H.: The Immunological Problems of Influenza, Practitioner 173:534-539 (Nov.) 1954.

68. Hamre, D.; Appel, J., and Loosli, C. G.: Viremia in Mice with Pulmonary Influenza A Virus Infections, J. Lab. & Clin. Med. 47:182-193 (Feb.) 1956.

69. Ginsberg, H. S.: Formation of Non-Infectious Influenza Virus in Mouse Lungs: Its Dependence upon Extensive Pulmonary Consolidation Initiated by the Viral Inoculum, J. Exper. Med. 100:581-603 (Dec.) 1954.

70. Mogabgab, W. J.; Dierkhising, O. C., and Phillips, I. A.: Isolation and Cytopathogenic Effect of Influenza B Viruses in Monkey Kidney Cultures, Proc. Soc. Exper. Biol. & Med. 89:654-659 (Aug.-Sept.) 1955.

71. Liu, O. C.; Blank, H.; Spizizen, J., and Henle, W.: The Incorporation of Radioactive Phosphorus into Influenza Virus, J. Immunol. 73:415-425 (Dec.) 1954.

72. Pilcher, K. S., and others: Inhibition of Multiplication of Lee Influenza Virus by Canavanine, Proc. Soc. Exper. Biol. & Med. 88:79-86, (Jan.) 1955.

73. Green, M., and Stahmann, M. A.: Virus Inhibitory Activity of Polyvinylamine, Proc. Soc. Exper. Biol. & Med. 87:507-509 (Dec.) 1954.

74. Horstmann, D. M.; McCollum, R. W., and Mascola, A. D.: The Incidence of Infection Among Contacts of Poliomyelitis Cases, J. Clin, Invest. 34:1573-1580 (Oct.) 1955.

74a. Wehrle, P. F.: The Risk of Poliomyelitis Infections Among Exposed Hospital Personnel, Pediatrics 17:237-246 (Feb.) 1956.

75. Siegel, M., and Greenberg, M.: Comparative Fatality of Poliomyelitis in Families with Single and Multiple Cases, J. A. M. A. 157:1080-1083, (March 26) 1955.

76. Sabin, A. B., and Fieldsteel, H. A., in Sixth International Congress of Microbiology, 1953, Vol. 2, p. 373.

77. Bartell, P., and Klein, M.: Neutralizing Antibody to Viruses of Poliomyelitis in Sera of

Domestic Animals, Proc. Soc. Exper. Biol. & Med. 90:597-601 (Dec.) 1955.

78. Lawrence R., and Carmichael, D. B.: Myocarditis in Acute Poliomyelitis, U. S. Armed Forces M. J. 6:1817-1824 (Dec.) 1955.

79. Gebhardt, L. P., and Bachtold, J. G.: Chemoprophylaxis and Chemotherapy of Experimental Poliomyelitis, Proc. Soc. Exper. Biol. & Med. 88:103-107 (Jan.) 1955.

80. Barski, G.; Robineaux, R., and Endo, M.: Phase Contrast Cinematography of Cellular Lesion Produced by Poliomyelitis Virus in Vitro, Proc. Soc. Exper. Biol. & Med. 88:57-59 (Jan.) 1955.

81. Robertson, H. E.; Brunner, K. T., and Syverton, J. T.: Propagation in Vitro of Poliomyelitis Viruses: VII. pH Change of HeLa Cell Cultures for Assay, Proc. Soc. Exper. Biol. & Med. 88:119-122 (Jan.) 1955.

82. Lipton, M. M., and Steigman, A. J.: A Simplified Colorimetric Test for Poliomyelitis Virus and Antibody, Proc. Soc. Exper. Biol. & Med. 88:114-118 (Jan.) 1955.

83. Chanock, R. M.: Cytopathogenic Effect of Newcastle Virus in Monkey Kidney Cultures and Interference with Poliomyelitis Viruses, Proc. Soc. Exper. Biol. & Med. 89:379-381 (July) 1955.

84. Communicable Diseases, Washington News, J. A. M. A. 160:14 (Jan. 21) 1956.

85. Deleted by the author.

86. Anderson, O. L.: Progress Report on the Poliomyelitis Vaccine Program, J. A. M. A. 159:1522-1525 (Dec. 17) 1955.

87. Langmuir, A. D.; Nathanson, N., and Hall, W. J.: Surveillance of Poliomyelitis in the United States in 1955, Am. J. Pub. Health, 46:75-88 (Jan.) 1956.

88. Pope, A. S., and others: Evaluation of Poliomyelitis Vaccination in Massachusetts, New England J. Med. 254:110-117 (Jan. 19) 1956.

89. Deleted by the author.

90. Symposium on Poliomyelitis, Foreign Letters (Switzerland), J. A. M. A. 159:1234-1235 (Nov. 19) 1955.

91. Tyrrell, D.; Keeble, S. A., and Wood, W.: Antigenicity Studies on Salk-Type Poliomyelitis Vaccine, Brit. M. J. 1:598-601 (March 17) 1956.

92. The Devil's Advocate and the 1955 Salk Poliomyelitis Vaccine Program: A Contribution Toward an Objective Evaluation, Bull. Am. A. Pub. Health Physicians 2:3-8 (Nov.) 1955.

93. Deleted by the author.

94. Scope 1:1 (Jan. 18) 1956 (published by The Upjohn Company, Kalamazoo, Mich.).

95. Sabin, A. B.: Behavior of Chimpanzee-Avirulent Poliomyelitis Viruses in Experimentally Infected Human Volunteers, Am. J. M. Sc. 230:1-8 (July) 1955.

96. Koprowski, A., and others: Clinical Investigations on Attenuated Strains of Poliomyelitis Virus: Use as a Method of Immunization of Children with Living Virus, J. A. M. A. 160:954-966 (March 17) 1956.

97. MacIver, D. P.: Vaccinia Versus Poliomyelitis? Lancet 1:226-228 (Feb. 4) 1956.

98. Measles, Leading Articles, Brit. M. J. 1:1018-1019 (April 23) 1955.

99. Bettag, O. L.; Plotke, F., and Sterling, H. M.: Effect of Gamma Globulin on Measles, Pub. Health Rep. 70:353-355 (April) 1955.

100. Gamma Globulin and Adult Serum for Measles, Foreign Letters (England), J.A.M.A. 157:744-745 (Feb. 26) 1955.

101. Steen, J.: Measles Encephalitis: Frequency, Mortality and Follow-Up Findings, Nord. med. 52:1468-1471 (Oct. 21) 1954.

102. Tompkins, V., and Macaulay, J. C.; A Characteristic Cell in Nasal Secretions During Prodromal Measles, J. A. M. A. 157:711 (Feb. 26) 1955.

103. Henle, G., and Deinhardt, F.: Propagation and Primary Isolation of Mumps Virus in Tissue Culture, Proc. Soc. Exp. Biol. & Med. 89:556-560 (Aug.-Sept.) 1955.

104. Odessky, L.; Newman, B., and Wein, G. B.: Congenital Varicella, New York J. Med. 54:2849-2852 (Oct. 15) 1954.

105. Simpson, R. E. H.: Studies on Shingles: Is the Virus Ordinary Chickenpox Virus? Lancet 2:1299-1302 (Dec. 25) 1954.

106. Adair, C. V.; Gauld, R. L., and Smadel, J. A.: Aseptic Meningitis, a Disease of Diverse Etiology: Clinical and Etiologic Studies on 854 Cases, Ann. Int. Med. 39:675-704 (Oct.) 1953.

107. Dascomb, H. E.; Adair, C. V., and Rogers, N.: Serologic Investigations of Herpes Simplex Virus Infections, J. Lab. & Clin. Med. 46:1-11 (July) 1955.

108. Kirby, W. M., and Evans, C. A.: Tissue Culture Isolation of Coxsackie Group B Viruses in Aseptic Meningitis, J. A. M. A. 159:743-746 (Oct. 22) 1955.

109. Javett, S. N., and others: Myocarditis in the Newborn Infant: Study of an Outbreak Associated with Coxsackie Group B Virus Infection in a Maternity Home in Johannesburg, J. Pediat. 48:1-22 (Jan.) 1956.

110. Sickles, G. M.; Mutterer, M.; Feorino, P., and Plager, H.: Recently Classified Types of Coxsackie Virus, Group A: Behavior in Tissue Culture, Proc. Soc. Exper. Biol. & Med. 90:529-531 (Nov.) 1955.

111. Eklund, C. M.; Kohls, G. M., and Brennan, J. M.: Distribution of Colorado Tick Fever and Virus-Carrying Ticks, J. A. M. A. 157:335-337 (Jan. 22) 1955.

112. Kalter, S. S.; Prier, J. E., and Prior, J. T.: Recent Studies on the Diagnosis of Cat Scratch Fever, Ann. Int. Med. 42:562-573 (March) 1955.

113. Gifford, H.: Skin-Test Reactions to Cat-Scratch Disease Among Veterinarians, A. M. A. Arch. Int. Med. 95:828-833 (June) 1955.

114. Hoagland, R. J.: The Transmission of Infectious Mononucleosis, Am. J. M. Sc. 229:262-272 (March) 1955.

115. Elton, N. W.; Romero, A., and Trejos, A.: Clinical Pathology of Yellow Fever, Am. J. Clin. Path. 25:135-146 (Feb.) 1955.

116. Frederiksen, H.: Historical Evidence for Interference Between Dengue and Yellow Fever, Am. J. Trop. Med. 4:483-491 (May) 1955.

117. Neefe, J. R., and others: Prevalence and Nature of Hepatic Disturbance Following Acute Viral Hepatitis with Jaundice, Ann. Int. Med. 43:1-32 (July) 1955.

118. Saphir, O.; Amromin, G. D., and Yokoo, H.: Myocarditis in Viral (Epidemic) Hepatitis, Am. J. M. Sc. 231:168-176 (Feb.) 1956.

119. Huber, T. E., and Wiley, A. T.: Cortisone in the Treatment of Infectious Hepatitis, Ann. Int. Med. 42:1011-1025 (May) 1955.

120. Pollard, M., and Diserens, L. T.: Cytological Response to Infectious Hepatitis Specimens in Embryonated Eggs, Proc. Soc. Exper. Biol. & Med. 88:236-238 (Feb.) 1955.

121. Mayer, C. F.: European Outbreaks of the Far-Eastern (Korean) Type of Epidemic Hemorrhagic Fever (EHF), Mil. Med. 117:502-507 (Dec.) 1955.

122. Germer, W. D.: Hemorrhagic Fevers, with Special Consideration of the Hemorrhagic Fevers Occurring in Korea, Deutsche med. Wchnschr. 80:1717-1721 (Nov. 25) 1955.

123. La Veck, G. D.; Winn, J. F., and Welch, S. F.: Inapparent Infection with Western Equine Encephalitis Virus: Epidemiologic Observations, Am. J. Pub. Health 45:1409-1416 (Nov.) 1955.

124. Holden, P.: Recovery of Western Equine Encephalomyelitis Virus from Naturally Infected English Sparrows of New Jersey, 1953, Proc. Soc. Exper. Biol. & Med. 88:490-492 (March) 1955.

125. Holden, P.; Miller, B. J., and Jobbins, D. M.: Isolations of Eastern Equine Encephalomyelitis Virus from Mosquitoes (Culiseta Melanura) Collected in New Jersey, 1953, Proc. Soc. Exper. Biol. & Med. 87:457-459 (Nov.) 1954.

126. Yesnick, L.: Central Nervous System Complications of Primary Atypical Pneumonia, A. M. A. Arch. Int. Med. 97:93-98 (Jan.) 1956.

127. Hall, J. B.: Rabies Control, GP 11:81-85 (April) 1955.

128. Virus of Bats Antigenically Related to St. Louis Encephalitis, Reports and Letters, Science 123:227-228 (Feb. 10) 1956.

129. Large Outbreak of Gastroenteritis, Medical News, J. A. M. A. 157:1137 (March 26) 1955.

129a. Higgins, A. R.: The Case for Viral Diarrheal Disease, Editorial, Am. J. Med. 21:157-160 (Aug.) 1956.

130. Gordon, I.: The Nonamebic Nonbacillary Diarrheal Disorders, Am. J. Trop. Med. 4:739-755 (July) 1955.

131. Zhdanov, V. M.; Havrylov, V. I., and Muzhenkova, N. P.: Concerning the Etiology of Viral Gastroenteritis, Microbiol. Epidemiol. & Immunol., No. 6, pp. 78-85, 1955.

132. Ramos-Alvarez, M., and Sabin, A. B.: Intestinal Viral Flora of Healthy Children Demonstrable by Monkey Kidney Tissue Culture, Am. J. Pub. Health 46:295-299 (March) 1956.

133. Horstmann, D. M.: Endemic Virus Infections in Egypt: Isolation of Poliomyelitis Viruses and other Tissue Culture Pathogenic Agents from Jnfants, Fed. Proc. 14:466 (March) 1955.

134. Enteric Cytopathogenic Human Orphan (ECHO) Viruses, Reports and Letters, Science 122:1187-1188 (Dec. 16) 1955.

135. Immunization Against Viruses, Leading Articles, Brit. M. J. 2:186-187 (July 16) 1955.

136. Rustigian, R.; Johnston, P., and Reihart, H.: Infection of Monkey Kidney Tissue Cultures with Virus-like Agents, Proc. Soc. Exper. Biol. & Med. 88:8-16 (Jan.) 1955.

137. Innes, J. R. M.; McAdams, A. J., and Yevich, P.: Pulmonary Disease in Rats: A Survey with Comments on "Chronic Murine Pneumonia," Am. J. Path. 32:141-159 (Jan.-Feb.) 1956.

138. Wesselhoeft, C.: Acute Infectious Diseases in Pregnancy, Ann. Int. Med. 42:555-561 (March) 1955.

139. Updyke, E. L.; Moore, M. S., and Conroy, E.: Provisional New Type of Group A Streptococci Associated with Nephritis, Science 121:171-172 (Feb. 4) 1955.

140. Reed, R. W., and Matheson, B. H.: Experimental Nephritis Due to Type Specific Streptococci: I. The Effect of a Single Exposure to Type 12 Streptococci, J. Infect. Dis. 95:191-201 (Sept.-Oct.) 1954; II. The Effect of Repeated Exposure to Type 12 Streptococci, J. Infect. Dis. 95:202-212 (Sept.-Oct.) 1954.

141. Stevens, F. A.: Allergic Reactions in Sites Recurrently Infected with Hemolytic Streptococcus, Am. J. Med. 20:185-188 (Feb.) 1956.

142. Glaser, R. J.; Pesch, B. B., and Voege, B. N.: Immunity in Group A Streptococcal Infections: I. Non-Specific Protective Effect in Repeated Pulmonary Infections, Proc. Soc. Exper. Biol. & Med. 88:140-144 (Jan.) 1955.

143. Van Metre, T. E., Jr.: Pneumoccoccal Pneumonia Treated with Antibiotics: The Prognostic Significance of Certain Clinical Findings, New England J. Med. 251:1048-1052 (Dec. 23) 1954.

144. Shaw, A. B., and Fry, J.: Acute Infections

of the Chest in General Practice, Brit. M. J. 2:1577-1586 (Dec. 31) 1955.

145. Page, J. A.: Fatal Suppression of Symptoms During Hormone Therapy, J. Am. Geriatrics Soc. 3:890-892 (Nov.) 1955.

146. Pengelly, C. D. R.: Pneumococcal Meningitis: A Short Survey of 78 Patients in the Bristol Clinical Area, Brit. M. J. 1:870-874 (April 9) 1955.

147. Hall, B.; Dowling, H. F., and Kellow, W.: Successful Short-Term Therapy of Streptococcal Endocarditis with Penicillin and Streptomycin, Am. J. M. Sc. 230:73-81 (July) 1955.

148. Henriksen, E., and Neukirch, F.: The Treatment of Subacute Bacterial Endocarditis, Danish M. Bull. (No. 7) 2:208-213 (Dec.) 1955.

149. Taggart, S. R.: Gonorrhea Detection by Urine Examination, Pub. Health Rep. 70:245-247 (March) 1955.

150. Catanzaro, F. J., and others: Effect of Oxytetracycline Therapy of Streptococcal Sore Throat on the Incidence of Acute Rheumatic Fever, Ann. Int. Med. 42:345-357 (Feb.) 1955.

151. Morris, A. J.; Chamovitz, R.; Catanzaro, F. J., and Rammelkamp, C. H., Jr.: Prevention of Rheumatic Fever by Treatment of Previous Streptococcic Infections: Effect of Sulfadiazine, J. A. M. A. 160:114-116 (Jan. 14) 1956.

152. Rheumatic Fever Prevention, Pub. Health Rep. 70:373-377 (April) 1955.

153. Rheumatic Fever Management, Pub. Health Rep. 70:259-260 (March) 1955.

154. Finland, M.: Introductory Remarks on the Current Status of Antibiotic Therapy and the Outlook for Future Developments, Am. J. Med. 18:679-685 (May) 1955.

155. Miller, J. M., and Massell, B. F.: Studies of Bacterial Throat Flora During Chemoprophylaxis of Rheumatic Fever, New England J. Med. 254:149-154 (Jan. 26) 1956.

156. Wilson, M. G., and Schweitzer, M.: Pattern of Hereditary Susceptibility in Rheumatic Fever, Circulation 10:699-704 (Nov.) 1954.

157. Wedum, B. G., and Rhodes, P. H.: Differential Diagnosis of Rheumatic Fever in Office Practice, J. A. M. A. 157:981-986 (March 19) 1955.

158. Lustok, M. J., and Kuzma, J. F.: Rheumatic Fever Pneumonitis: A Clinical and Pathologic Study of 35 Cases, Ann. Int. Med. 44:337-357 (Feb.) 1956.

159. Treatment of Acute Rheumatic Fever in Children: A Co-Operative Clinical Trial of A.C.T.H., Cortisone, and Aspirin, Brit. M. J. 1:555-574 (March 5) 1955.

160. Massell, B. F.: Hormone Treatment of Rheumatic Carditis, Bull. Rheumat. Dis. 6:99-100 (Dec.) 1955.

161. Bunim, J. J.; Pechet, M. M., and Bollet, A. J.: Studies on Metacortandralone and Metacortandracin in Rheumatoid Arthritis: Antirheumatic Potency, Metabolic Effects, and Hormonal Properties, J. A. M. A. 157:311-318 (Jan. 22) 1955.

162. Boland, E. W.: Prednisone and Prednisolone as Suppressive Agents for Rheumatoid Arthritis, Bull. Rheumat. Dis. 6:107-108 (March) 1956.

163. The Effect of Cortisone and Related Steroids on the Carditis of Rheumatic Fever, Editorial, Ann. Int. Med. 44:426-431 (Feb.) 1956.

164. Ellis, L. B., and Harken, D. E.: The Clinical Results in First 500 Patients with Mitral Stenosis Undergoing Valvuloplasty, Circulation 11:637-646 (April) 1955.

165. Bergy, G. G., and Bruce, R. A.: Discrepancies Between Subjective and Objective Responses to Mitral Commissurotomy, New England J. Med. 253:887-891 (Nov. 24) 1955.

166. McKusick, V. A.: Rheumatic Restenosis of Mitral Valve: Report of a Case with Death Almost 5 Years After Mitral Valvulotomy, A. M. A. Arch. Int. Med. 95:557-562 (April) 1955.

167. Dalton, J. C.; Williams, B., and Atkins, L.: Staphylococcal Endocarditis After Mitral Valvulotomy: Report of 3 Cases, New England J. Med. 254:205-210 (Feb. 2) 1956.

168. Engleman, E. P.: The Annual Meeting of the American Rheumatism Association, Bull. Rheumat. Dis. 6:91-94 (Sept.) 1955.

169. Stollerman, G. H.; Lewis, A. J.; Schultz, I., and Taranta, A.: Relationship of Immune Response to Group A Streptococci to the Course of Acute, Chronic and Recurrent Rheumatic Fever, Am. J. Med. 20:163-169 (Feb.) 1956.

170. Taranta A., and Stollerman, G. H.: The Relationship of Sydenham's Chorea to Infection with Group A Streptococci, Am. J. Med. 20:170-175 (Feb.) 1956.

171. Morse, S. I.; Darnell, J. E., Jr.; Thomas, W. A., and Glaser, R. J.: Cardiac Lesions in Rabbits After Pharyngeal Infections with Group A Streptococci, Proc. Soc. Exper. Biol. & Med. 89:613-616 (Aug.-Sept.) 1955.

172. Denny, F. W., Jr., and Thomas, L.: Persistence of Group A Streptococci in Tissues of Rabbits After Infection, Proc. Soc. Exper. Biol. & Med. 88:260-263 (Feb.) 1955.

173. Dresner, E.: Aetiology and Pathogenesis of Rheumatoid Arthritis, Am. J. Med. 18:74-111 (Jan.) 1955.

174. Marked Decline in Tuberculosis Among Children, Statist. Bull. Metrop. Life Insur. Co. 36:5-8 (Nov.) 1955.

175. Walker, C. H. M.: Pulmonary Primary Tuberculosis in Childhood, Lancet 1:218-224 (Jan. 29) 1955.

176. Myers, J. A.; Gunlaugson, F. G.; Meyer-

ding, E. A., and Roberts, J.: Importance of Tuberculin Testing of School Children—A 28 Year Study, J. A. M. A. 159:185-190 (Sept. 17) 1955.

177. A Proposal for Reducing the Cost of Care of the Tuberculous in Countries of Limited Means, correspondence, Am. Rev. Tuberc. 73:444-445 (March) 1956.

178. Experiments with Isoniazid as a Preventive Measure Against Tuberculosis, Pub. Health Rep. 70:759-760 (Aug.) 1955.

179. Mass BCG Vaccination, Foreign Letters (Norway), J. A. M. A. 160:500 (Feb. 11) 1956.

180. Wallgren, A.: Should Mass Vaccination with BCG be Discontinued in Scandinavia? Acta pædiat. 44:237-253 (May) 1955.

181. Rosenthal, S. R.: Standardization and Efficacy of BCG Vaccination Against Tuberculosis: Twenty Year Study; A Critical Evaluation, J. A. M. A. 157:801-807 (March 5) 1955.

182. Stein, S. C., and Sokoloff, M. J.: Calcification of Regional Lymph Nodes Following BCG Vaccination, Am. Rev. Tuberc. 73:239-245 (Feb.) 1956.

183. New TB Vaccine, News of Science, Science 123:411 (March 9) 1956.

184. Muschenheim, C.: A Schema of Treatment in Tuberculosis, Am. Rev. Tuberc. 72:1-11 (July) 1955.

185. Overby, H. T., and Woliung, R. W.: Experiences in the Management of Long-Standing Chronic Cases of Pulmonary Tuberculosis Treated with Isoniazid for One Year, Dis. Chest 27:51-58 (Jan.) 1955.

186. Sweany, H. C.; Dunbar, F. P., and Wood, E.: The Problem of Bacterial Resistance in Antimicrobial Therapy of Tuberculosis, Dis. Chest 28:260-274 (Sept.) 1955.

187. Amberson, J. B.: Evaluation of the Present-Day Treatment of Pulmonary Tuberculosis, Ann. Int. Med. 43:1209-1217 (Dec.) 1955.

188. Ashby, M., and Grant, H.: Tuberculous Meningitis Treated with Cortisone, Lancet 1:65-66 (Jan. 8) 1955.

189. Gierson, H. W., and Marx, J. I.: Tuberculous Meningitis: The Diagnostic and Prognostic Significance of Spinal Fluid Sugar and Chloride, Ann. Int. Med. 42:902-908 (April) 1955.

190. Nesbit, R. M., and MacKinny, C. C.: Antibiotic Therapy of Urinary Tuberculosis: An Interval Report of 6 Years Experience, J. Urol. 72:296-303 (Sept.) 1954.

191. Lattimer, J. K.; Wechsler, H.; Spirito, A. L., and Whittle, G. T.: Treatment of Renal Tuberculosis with Triple-Drug Therapy: Use of a Combination of Streptomycin, Isoniazid, and Sodium Aminosalicylic Acid, J. A. M. A. 160:544-546 (Feb. 18) 1956.

192. Chaves, A. D., and others: The Prevalence of Streptomycin- and Isoniazid-Resistant Strains of Mycobacterium Tuberculosis in Patients with Newly Discovered and Untreated Active Pulmonary Tuberculosis, Am. Rev. Tuberc. 72:143-150 (Aug.) 1955.

193. Beck. F.: Infection with Drug-Resistant Tubercle Bacilli, Am. Rev. Tuberc. 72:151-157 (Aug.) 1955.

194. Tubercle Bacilli on the Streets, Foreign Letters (Turkey), J. A. M. A. 159:1051 (Nov. 5) 1955.

195. Isoniazid Resistance, Leading Articles, Lancet 1:238-239 (Jan. 29) 1955.

196. Dubos, R. J.: Effect of Metabolic Factors on the Susceptibility of Albino Mice to Experimental Tuberculosis, J. Exper. Med. 101:59-84 (Jan.) 1955.

197. van Zwanenberg, D., and Barry, M.: A Case of Sarcoidosis and 3 Cases of Atypical Tuberculosis in a Family, Lancet 1:483-485 (March 5) 1955.

198. The Liver in Sarcoidosis, Annotations, Lancet 1:374 (April 7) 1956.

199. Ban, B.: Hepatic Damage in Chronic Pulmonary Tuberculosis, Am. Rev. Tuberc. 72:71-90 (July) 1955.

200. Dodson, L. F.; Sanders, A. G., and Florey, H. W.: Observations on Tuberculous Lesions in a Transparent Chamber in the Rabbit's Ear, Brit. J. Exper. Path. 35:338-344 (Aug.) 1954.

201. Lack, C. H.; Chronic Tuberculous Infection in Experimental Animals, Am. Rev. Tuberc. 73:378-389 (March) 1956.

202. Timpe, A., and Runyon, E. H.: The Relationship of "Atypical" Acid-Fast Bacteria to Human Disease, J. Lab. & Clin. Med. 44:202-209 (Aug.) 1954.

203. Wilson, G. C., and Morton, D. E.: The Clinical Significance of Acid-Fast Bacilli Nonpathogenic for Guinea Pigs, Am. Rev. Tuberc. 73:351-361 (March) 1956.

204. Trends, Pub. Health Rep. 70:491 (May) 1955.

205. Benavides V., L.; Olson, B. H.; Varela, G., and Holt, S. H.: Treatment of Typhoid with Synnematin B: Preliminary Report, J. A. M. A. 157:989-994 (March 19) 1955.

206. Reimann, H. A., and Pang, T. L.: Chloramphenicol in Paratyphoid A: Observations with a Note on the Clinical Aspects of the Disease, A. M. A. Arch. Int. Med. 96:777-780 (Dec.) 1955.

207. Typhoid Infection, Medical News, J. A. M. A. 159:1314 (Nov. 26) 1955.

208. Gayler, G. E.; MacCready, R. A.; Reardon, J. P., McKernan, B. F.: An Outbreak of Saimonellosis Traced to Watermelon, Pub. Health Rep. 70:311-313 (March) 1955.

209. Galton, M. M.; Lowery, W. D., and Hardy, A. V.: Salmonella in Fresh and Smoked

Pork Sausage, J. Infect. Dis. 95:233-235 (Nov.-Dec.) 1954.

210. Galton, M. M.; Smith, W. V.; McElrath, H. B., and Hardy, A. V.: Salmonella in Swine, Cattle and Environment of Abattoirs, J. Infect. Dis. 95:236-245 (Nov.-Dec.) 1954.

211. Anderson, A. S.; Bauer, H., and Nelson, C. B.: Salmonellosis Due to Salmonella Typhimurium with Easter Chicks as Likely Source, J. A. M. A. 158:1153-1155 (July 30) 1955.

212. Kunz, L. J., and Ouchterlony, O. T. G.: Salmonellosis Originating in a Hospital: A Newly Recognized Source of Infection, New England J. Med. 253:761-763 (Nov. 3) 1955.

213. Higgins, A. R.; Floyd, T. M., and Kader, M. A.: Studies in Shigellosis: III. A Controlled Evaluation of a Monovalent Shigella Vaccine in a Highly Endemic Environment, Am. J. Trop. Med. 4:281-288 (March) 1955; IV. A Controlled Trial of Sulfadiazine, Dihydrostreptomycin and Oxytetracycline as Long Term Prophylaxis Agents in a Highly Endemic Environment for Shigellosis, Am. J. Trop. Med. 4:289-300 (March) 1955.

214. Ghaffar, Y. A. E., and Ghaffar, M. A. E.: Atypical Chronic Intestinal Shigellosis, Am. J. Trop. Med. 4:301-309 (March) 1955.

215. Jones, H. L.; Cassis, G.; Floyd, T. M., and Mansour, N. S.: Amebiasis: Controlled Linear Studies on Nondysenteric and Mild Hepatic Forms in Egyptians, Ann. Int. Med. 42:763-785 (April) 1955.

216. Studies on Brucellosis, Pub. Health Rep. 70:214-217 (Feb.) 1955.

217. Levinson, A.; Marske, R. L., and Shein, M. K.: Tetanus in Heroin Addicts, J. A. M. A. 157:658-660 (Feb. 19) 1955.

218. Cole, A. C. E., and Robertson, D. H. H.: Chlorpromazine in the Management of Tetanus, Lancet 2:1063-1064 (Nov. 19) 1955.

219. Anwar, A. A., and Turner, T. B.: Antibiotics in Experimental Tetanus: In Vitro and in Vivo Studies, Bull. Johns Hopkins Hosp. 98:85-101 (Feb.) 1956.

220. Chemotherapy of Leprosy, Letters to the Editor, Lancet 1:101 (Jan. 8) 1955.

221. Powell, C. S., and Swan, L. L.: Leprosy: Pathologic Changes Observed in 50 Consecutive Necropsies, Am. J. Path. 31:1131-1148 (Nov.-Dec.) 1955.

222. Larson, C. L.; Wicht, W., and Jellison, W. L.: A New Organism Resembling P. Tularensis Isolated from Water, Pub. Health Rep. 70:253-258 (March) 1955.

223. Ransom, J. P.; Quan, S. F.; Hoggan, M. D., and Omi, G.: Antigenic Comparisons of Strains of Pasteurella Pestis, Proc. Soc. Exper. Biol. & Med. 88:173-178 (Feb.) 1955.

224. Low, N. L.: Electroencephalographic Studies Following Pertussis Immunizations, J. Pediat. 47:35-39 (July) 1955.

225. Mendell, H. E.; Foxworthy, D. L., and Wornas, C. G.: Chemotherapy of Chancroid: Clinical Observations in 87 Cases, Am. J. Syph. 38:483-486 (Sept.) 1954.

226. Alston, J. M.: Necrobacillosis in Great Britain, Brit. M. J. 2:1524-1528 (Dec. 24) 1955.

227. Garrod, L. P.: Sensitivity of 4 Species of Bacteroides to Antibiotics, Brit. M. J. 2:1529-1531 (Dec. 24) 1955.

228. Freter, R.: The Fatal Enteric Cholera Infection in the Guinea Pig, Achieved by Inhibition of Normal Enteric Flora, J. Infect. Dis. 97:57-65 (July-Aug.) 1955.

229. Emmons, C. W., and others: Histoplasmosis: Proved Occurrence of Inapparent Infection in Dogs, Cats and Other Animals, Am. J. Hyg. 61:40-44 (Jan.) 1955.

230. Furcolow, M. L.; Menges, R. W., and Larsh, H. W.: An Epidemic of Histoplasmosis Involving Man and Animals, Ann. Int. Med. 43:173-181 (July) 1955.

231. Parrott, T., Jr.; Taylor, G.; Poston, M. A., and Smith, D. T.: An Epidemic of Histoplasmosis in Warrenton, North Carolina, South. M. J. 48:1147-1150 (Nov.) 1955.

232. Spicknall, C. G.; Ryan, R. W., and Cain, A.: Laboratory-Acquired Histoplasmosis, New England J. Med. 254:210-214 (Feb. 2) 1956.

233. Malady is Linked to Rare Oilbirds, New York Times, Feb. 5, 1956, p. 15.

234. Silverman, F. N.; Schwarz, J.; Lahey, M. E., and Carson, R. P.: Histoplasmosis, Am. J. Med. 19:410-459 (Sept.) 1955.

235. Schwartz, B.: Histoplasmosis of Lungs, A. M. A. Arch. Int. Med. 94:970-994 (Dec.) 1954.

236. Straub, M., and Schwarz, J.: The Healed Primary Complex in Histoplasmosis, Am. J. Clin. Path. 25:727-741 (July) 1955.

237. Puckett, T. F.: Pulmonary Histoplasmosis, Am. J. Surg. 90: 92-100 (July) 1955.

238. Sutliff, W. D., and Campbell, C. C.: Serologic Screening for Systemic Mycoses, Tr. Conf. Chemother. Tuberc. 14:285-288, 1955.

239. Brasher, C. A., and Furcolow, M. L.: Chronic Cavitary Histoplasmosis as a Problem in Tuberculosis Sanitaria, Tr. Conf. Chemother. Tuberc. 14:288-294, 1955

240. Shapiro, J. L.; Lux, J. J., and Sprofkin, B. E.: Histoplasmosis of the Central Nervous System, Am. J. Path. 31:319-336 (March-April) 1955.

241. Therapy of Fungus Diseases, edited by T. H. Sternberg and V. D. Newcomer, Boston, Little, Brown & Company, 1955, pp. 1-337.

242. Science News, Science 121:123 (Jan. 28) 1955.

243. Egeberg, R. O., and Ely, A. F.: Coccidiodes

Immitis in the Soil of the Southern San Joaquin Valley, Am. J. M. Sc. 231:151-154 (Feb.) 1956.

244. Fiese, M. J.; Cheu, S., and Sorensen, R. H.: Mycelial Forms of Coccidioides Immitis in Sputum and Tissues of the Human Host, Ann. Int. Med. 43:255-270 (Aug.) 1955.

245. Smith, C. E.; Saito, M. T., and Simons, S. A.: Pattern of 39,500 Serologic Tests in Coccidioidomycosis, J. A. M. A. 160:546-552 (Feb. 18) 1956.

246. Dennis, J. L., and Hansen, A. E.: Coccidioidomycosis in Children, Pediatrics 14:481-494 (Nov.) 1954.

247. Cotton, B. H.; Paulsen, G. A., and Birsner, J. W.: Surgical Considerations in Pulmonary Coccidioidomycosis: Report of 100 Cases, Am. J. Surg. 90:101-106 (July) 1955.

248. Baer, R.; Rosenthal, S. A.; Rogachefsky, H., and Litt, J. Z.: Newer Studies on the Epidemiology of Fungous Infections of the Feet, Am. J. Pub. Health 45:784-790 (June) 1955.

249. Baer, R. L.; Rosenthal, S. A.; Litt, J. Z., and Rogachefsky, H.: Experimental Investigations on Mechanism Producing Acute Dermatophytosis of Feet, J. A. M. A. 160:184-190 (Jan. 21) 1956.

250. Schaberg, A.; Hildes, J. A., and Wilt, J. C.: Disseminated Candidiasis, A. M. A. Arch. Int. Med. 95:112-117 (Jan.) 1955.

251. Levy, E. S., and Cohen, D. B.: Systemic Moniliasis and Aspergillosis Complicating Corticotropin Therapy, A. M. A. Arch. Int. Med. 95: 118-122 (Jan.) 1955.

252. Kelley, G. W., Jr.: Intestinal Parasitism in an Irrigated Community of Western Nebraska, Am. J. Trop. Med. 4:901-907 (Sept.) 1955.

253. Mackie, T. T., and others: Intestinal Parasitic Infections in Forsyth County, North Carolina: II. Amebiasis, a Familial Disease, Ann. Int. Med. 43:491-503 (Sept.) 1955.

254. Nelson, T. L.; Anderson, H. H., and Thomas, O.: Amebic Hepatitis: Laboratory Findings and Treatment with Erythromycin, Am. J. Trop. Med. 4:812-821 (Sept.) 1955.

255. Kean, B. H.: Amebic Hepatitis: Absence of Diffuse Lesions at Autopsy and in Biopsies, A. M. A. Arch. Int. Med. 96:667-673 (Nov.) 1955.

256. Radke, R. A.: Ameboma of the Intestine: An Analysis of the Disease as Presented in 78 Collected and 41 Previously Unreported Cases, Ann. Int. Med. 43:1048-1066 (Nov.) 1955.

257. Villarejos, V. M.: Treatment of Amebiasis with Erythromycin, Am. J. Trop. Med. 4:699-704 (July) 1955.

258. Anderson, H. H.; Nelson, T. L.; Carbono, C., and Diaz, J.: Erythromycin Stearate Against Systemic Amebiasis in Colombia, Am. J. Trop. Med. 4:693-698 (July) 1955.

259. Phillips, B. P., and others: Studies on the Ameba-Bacteria Relationship in Amebiasis: Comparative Results of the Intracecal Inoculation of Germfree, Monocontaminated, and conventional Guinea Pigs with Entamoeba Histolytica, Am. J. Trop. Med. 4:675-692 (July) 1955.

260. Arnold, J., and others: The Effect of Continuous and Intermittent Primaquine Therapy on the Relapse Rate of Chesson Strain Vivax Malaria, J. Lab. & Clin. Med. 44:429-428 (Sept.) 1954.

261. Creyx, M.; Leng-Lévy, J., and Laborie, G.: Problem of Late Revivescence of Human Malaria, Presse méd. 63:877-878 (June 8) 1955.

262. Coutts, W. E., and others: Trichomonas Vaginalis Infection in the Male, Brit. M. J. 2:885-889 (Oct. 8) 1955.

263. Feldman, H. A., and Miller, L. T.: Toxoplasma Epidemiological Serology, Fed. Proc. 14:462 (March) 1955.

264. Beverly, J. K. A.; Skipper, E., and Marshall, S. C.: Acquired Toxoplasmosis, with a Report of a Case of Laboratory Infection, Brit. M. J. 1:577-578 (March 5) 1955.

265. Thorson, R. E.; Bailey, W. S.; Hoerlein, B. F., and Siebold, H. R.: A Report of a Case of Imported Visceral Leishmaniasis of a Dog in the United States, Am. J. Trop. Med. 4:18-22 (Jan.) 1955.

266. Heisch. R. B.: Studies in Leishmaniasis in East Africa: I. The Epidemiology of an Outbreak of Kala-Azar in Kenya, Tr. Roy. Soc. Trop. Med. & Hyg. 48:449-469 (Nov.) 1954.

267. Shanbrom, E.; Minton, R.; Lester, C., and Correa, J. L.: Visceral Manifestations of American Mucocutaneous Leishmaniasis, Am. J. Med. 20:145-152 (Jan.) 1956.

268. Woody, N. C., and Woody, H. B.: American Trypanosomiasis (Chagas' Disease): First Indigenous Case in the United States, J. A. M. A. 159:676-677 (Oct. 15) 1955.

269. McCroan, J. E.; Ramsey, R. L.; Murphy, W. J., and Dick, L. S.: The Status of Rocky Mountain Spotted Fever in the Southeastern United States, Pub. Health Rep. 70:319-325 (March) 1955.

270. Gould, D. J., and Miesse, M. L.: Recovery of a Rickettsia of the Spotted Fever Group from Microtus Pennsylvanicus from Virginia, Proc. Soc. Exper. Biol. & Med. 85:558-561 (April) 1954.

271. Parker, R. T., and others: Persistence of Rickettsia Rickettsii in a Patient Recovered from Rocky Mountain Spotted Fever, J. Immunol. 73:383-386 (Dec.) 1954.

272. Schaefer, G. L.; Friedman, M., and Lewis, C.: The Incidence of Epidemic Typhus Antibodies in Individuals Born in Eastern Europe, Ann. Int. Med. 42:979-982 (May) 1955.

273. Gentry, J. T.; Nitousky, H. M., and Michael, M., Jr.: Studies on the Epidemiology of Sarcoidosis in the United States: The Relationship

to Soil Areas and to Urban-Rural Residence, J. Clin. Invest. 34:1839-1856 (Dec.) 1955.

274. Wheeler, A. H.; Van Goor, K., and Curtis, A. C.: Treponemal Immobilization and Standard Test Reactions in Suspected Biologic False Positive Sera, Am. J. Syph. 38:437-446 (Sept.) 1954.

275. Wilkinson, A. E., and Sequeira, P. J. L.: Studies on the Treponemal Immobilization Test: III. Use of the TPI as a Verification Test in Suspected Latent Syphilis, Brit. J. Ven. Dis. 31:143-154 (Sept.) 1955.

276. Anderson, T. R., and Zimmerman, L. E.: Relapsing Fever in Korea: A Clinicopathologic Study of 11 Fatal Cases with Special Attention to Association with Salmonella Infections, Am. J. Path. 31:1083-1110 (Nov.-Dec.) 1955.

277. Magath, T. B., and Thompson, J. H., Jr.: The Effect of Irradiation of Trichinella Spiralis on Immunity and Its Public Health Implication, Am. J. Trop. Med. 4:941-946 (Sept.) 1955.

278. "Chronic Appendicitis," Leading Articles, Brit. M. J. 1:776-777 (March 26) 1955.

279. Siniscal, A. A.: The Trachoma Story, Pub. Health Rep. 70:497-507 (May) 1955.

280. Schultz-Haudt, S. D., and Scherp, H. W.: Lysis of Collagen by Human Gingival Bacteria, Proc. Soc. Exper. Biol. & Med. 89:697-799 (Aug.-Sept.) 1955.

281. Routh, C. F.; McCroan, J. E., Jr., and Hames, C. G.: Three Cases of Human Infection with Isospora in Georgia, Am. J. Trop. Med. 4:1-8 (Jan.) 1955.

282. Epidemic in London Hospital, Foreign Letters (England), J. A. M. A. 159:700-701 (Oct. 15) 1955.

283. New Febrile Disease, Foreign Letters (Peru), J. A. M. A. 159:706 (Oct. 15) 1955.

284. Chancey, R. L., and Zatz, L. M.: Sporadic Acute Anicteric Hepatitis Associated with Upper Respiratory Infection, J. A. M. A. 158:1013-1016 (July 23) 1955.

285. Gartman, E.: An Outbreak of Acute Epididymitis Associated with Pneumonitis, U. S. Armed Forces M. J. 6:981-982 (July) 1955.

286. Beutler, E., and Dern, R. J.: Previously Unrecognized Transmissible Agent in Human Blood: Experimental and Clinical Studies, J. A. M. A. 159:989-994 (Nov. 5) 1955.

287. Murray, E. G. D.: A Surmise on Some Trends in Bacteriology, Lancet 1:221-224 (Jan. 30) 1954.

288. Kilbourne, E. D.: Influence of Cortisone on Experimental Viral Infection: II. Effects on Antibody Formation and Acquired Immunity, Proc. Soc. Exp. Biol. & Med. 90:685-687 (Dec.) 1955.

289. Thomas, L.: Cortisone, ACTH and Infection, Bull. New York Acad. Med. 31:485-499 (July) 1955.

290. Wagner, H. N., Jr., and others: The Effect of Hydrocortisone upon the Course of Pneumococcal Pneumonia Treated with Penicillin, Bull. Johns Hopkins Hosp. 98:197-215 (March) 1956.

291. Kass, E. H., and Finland, M.: Adrenocortical Hormones in Infection and Immunity, Ann. Rev. Microbiol. 7:361-388, 1953.

292. Roantree, R. J., and Rantz, L. A.: Clinical Experience with the C-Reactive Protein Test, A. M. A. Arch. Int. Med. 96:674-682 (Nov.) 1955.

293. Stein, E., and Smith, J. M.: C-Reactive Protein in the Acute Phase of the Common Contagious Diseases, A. M. A. J. Dis. Child. 91:150-152 (Feb.) 1956.

294. Shetlar, M. R.; Bullock, J. A.; Shetlar, C. L., and Payne, R. W.: Comparison of Serum C-Reactive Protein, Glycoprotein and Seromucoid in Cancer, Arthritis, Tuberculosis and Pregnancy, Proc. Soc. Exper. Biol. & Med. 88:107-109 (Jan.) 1955.

295. Anaerobic Cocci, Annotations, Lancet 1:293-294 (Feb. 5) 1955.

296. Carpenter, C. M.; Howard, D. H., and Lehman, E. L.: Preliminary Characterization of a Group of Unidentified Pleomorphic Bacteria Isolated from Blood and Other Tissues, J. Lab. & Clin. Med. 47:194-202 (Feb.) 1956.

297. Kassell, R., and Rottino, A.: Significance of Diphtheroids in Malignant Disease Studied by Germ-Free Techniques: Reevaluation in Hodgkin's Disease, Lymphoma, and Mouse Carcinoma, A. M. A. Arch. Int. Med. 96:804-808 (Dec.) 1955.

298. Bearn, A. G.; Jacobs, K., and McCarty, M.: Pasteurella Multocida Septicemia in Man, Am. J. Med. 18:167-168 (Jan.) 1955.

299. Stokes, E. J.: Human Infection with Pleuropneumonia-like Organisms, Lancet 1:276-279 (Feb. 5) 1955.

300. Wood, E. E.: Brucellosis as a Hazard of Blood Transfusion, Brit. M. J. 1:27-28 (Jan. 1) 1955.

301. Braude, A. I.: Carey, F. J., and Siemienski, J.: Studies of Bacterial Transfusion Reactions from Refrigerated Blood: The Properties of Cold-Growing Bacteria, J. Clin. Invest. 34:311-325 (Feb.) 1955.

302. Schostok, P., and Knoll, K. H.: Etiology of Transfusion Disturbances of Bacterial Origin, Chirurg 26:491-493 (Nov.) 1955.

303. Wetterlow, L. H.; Kay, F. H., and Edsall, G.: Missed Contaminations in Biologic Products: The Role of Psychrophilic Bacteria, J. Lab. & Clin. Med. 43:411-421 (March) 1954.

304. Mika, L. A., and others: Studies on Mixed Infection: I. Brucellosis and Q Fever, Proc. Soc. Exper. Biol. & Med. 87:500-507 (Dec.) 1954.

305. Genetic Recombination in Bacteria, Reports and Letters, Science 122:920 (Nov. 11) 1955.

Books

EDITED BY WILLIAM B. BEAN, M.D.

BOOK REVIEWS

Ciba Foundation Symposium on Experimental Tuberculosis: Bacillus and Host, with an Addendum on Leprosy. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., and Margaret P. Cameron, M.A., A.B.L.S. Price, $9. Pp. 376, with 69 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1955.

This volume contains 28 separate articles on the subjects of tuberculosis and leprosy. These papers were presented as a part of the Ciba Foundation Symposium on the tubercle bacillus and the reaction of tissues to tuberculous infection. Each paper is followed by the remarks of each of the discussants.

The enumeration of the papers and the authors is not practical. However, in this volume the following general subjects are covered. The nature and biological activity of the chemical substances isolated from the tubercle bacilli; the biochemical factors which are involved in resistance to infection by tubercle bacilli; the antigenic activity of various chemical fractions of tubercle bacilli; the nature of tuberculin hypersensitivity; the nature of immunity to tuberculosis, and the influence of a variety of factors on resistance and immunity to tuberculosis. Finally, there are four papers on leprosy, which summarize some of the information on the host parasite relationship in this disease.

In general this is a book which would be of great value to research workers in the field. Not only are the individual points of view on the subjects covered of interest, but reasonably good summaries of information in the included areas are given. The remarks of the discussants provide interesting reading and serve to illustrate vividly the perplexing nature of many of the problems concerned with the host-parasite relationship in tuberculosis. However, as might be expected from the fact that only a few investigators attended this meeting, much important material on the tubercle bacillus and the reaction of the host to tuberculous infection is missing.

GUY P. YOUMANS, M.D.

The Morphology of Human Blood Cells. By L. W. Diggs, M.A., M.D.; Dorothy Sturm, and Ann Bell, B.A. Price $12. Pp. 181, with color plates and figures. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia, 1956.

This book adequately fulfills all requirements expected of an atlas on the morphology of the blood cells as observed in the Wright's method of staining. The color plates probably reproduce the true color quality of the stained cells as well as can be done by painting in water color. The material is limited to smears of human blood and bone marrow, and the atlas, therefore, will find its principal use in the clinical laboratory. Quite properly in a volume of this type, no attempt is made to supplement the descriptions of the cells by a treatise on the diseases of the blood. The book is recommended for students in hematology, technicians, and those physicians who find it useful to refer to a publication of this type. The cost and quality should make it highly competitive with similar productions now available.

BRUCE K. WISEMAN, M.D.

W. W. Francis, Tributes from His Friends on the Occasion of the 35th Anniversary of the Osler Society of McGill University, Montreal. Price, not given. Page Printing Company, Montreal, Canada, 1956.

A firmly entrenched human tradition is to honor one's fellow man by occasions of celebration and hero worship. In our time of widespread neurosis and frustration, the capacity for admiration seems benumbed, much as the capacity for wonder, for the mere expression of curiosity, is bred out of us in spite of our system of education. In our time praise and

admiration are reserved for those who have died. It is rare for hero worship to find as elegant and delightful an expression for the living as is set forth in the tributes to W. W. Francis. In ways which far exceed the usual faint feeling of kinship of cousins, Francis, Osler's cousin, has come to embody the Osler tradition. In this book of praise and honor from his friends, is set forth in great detail Francis' devoted work as a student who completed the "Bibliotheca Osleriana" in a way which could never have been done without that devotion and grace which is true scholarship. Then he supervised the actual transfer of the books to the present Osler shrine, in Montreal. Since then he has presided as the benevolent but never trifling custodian of the Osler library—alert for any help he might bring the seeker, the student, or the admirer. How he has managed to be a comfort to the true student, a monument of bibliographic wisdom, but a tyrant against error we glimpse in this charming book which should be in all medical libraries.

WILLIAM B. BEAN, M.D.

Textbook of Occupational Therapy with Chief Reference to Psychological Medicine. By Eamon O'Sullivan. Price, $10. Pp. 319. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1955.

As the title implies, this is a standard text intended for use by occupational therapy students. Its content is quite basic. A brief history of the subject is presented, along with the aims and principals of this type therapy. One section covers the formation and operation of an occupational therapy unit in a general hospital. Another discusses those individual crafts that may be employed. The psychological aspects of this type therapy are reviewed. In this connection there is a section devoted to mental disease which is primarily descriptive and very fundamental. This book probably does not possess any marked advantages over those of this nature already in print. Its value is somewhat limited to occupational therapy students or to those in hospital administration.

W. HUMMEL, M.D.

Aspects of Allergy Research. Edited by D. Harley and P. Kallós. Price, $6.50. Pp. 198, with 76 illustrations. S. Karger A.G., Arnold Böcklinstrasse 25, Basel, Switzerland, 1955.

This booklet is a collection of twenty papers read at the first symposium of the Collegium Internationale Allergologicum in London, October, 1954. The subject material is diversified, but almost half of the papers deal with histamine, antihistaminics, or adrenal steroids. These are comprehensive and well supported by bibliographic and original data.

The immunological mechanisms in allergic disease are reviewed by Prausnitz. It is evident that only limited advances have been made in identification and characterization of the reagin since his historic demonstration of its skin-sensitizing characteristic by passive transfer in 1921. The absence of a reference to the work of Cooke and Loveless in his discussions of the blocking antibody is conspicuous in an otherwise well-documented paper. This is especially so, since he made the statement that blocking antibodies have a higher affinity for the cell than the reagins, which is contrary to the extensive studies of Cooke and Loveless, showing the blocking antibody lacked cell affinity.

In his discussion of serological problems in allergy, Coombs presented a preliminary report on the development and limitations of a method with theoretical capabilities of detecting the reagin in vitro. This gives promise of capturing this elusive antibody in the test tube.

Freeman reviews his clinical experiences with desensitization by pollen extract inoculation, which he has followed since its inception in clinical practice in 1911.

Mayer, in a comprehensive and lucid dissertation, pointed out the importance of the portal of entry of an allergen in determining whether the delayed or immediate type of allergic state develops.

In my opinion, the paper entitled "The Comprehensive Management of Patients Suffering Food-induced Allergies" does not qualify for a place under the title "Aspects of Allergy Research." The very controversial concept of "variable food allergies" is discussed in general terms, with a few intermingled case histories. Since this entity defies immunological proof, the author should have presented data of placebo-controlled clinical experimentation to support his observations. Without it he cannot expect observations like the following to go

unchallenged. "I have seen patients with rheumatic fever who had concomitant allergic food-induced musculoskeletal syndrome—and elimination of offending foods lessened the apparent severity of the ailment and reintroduction of the offending foods worsened it."

Other subjects covered in this collection are collagen disease, allergenicity of gelatin, thrombocytes in allergic disease, cell phospholipids in allergic tissue, and the rate of absorption of food allergens measured by the Prausnitz and Kustner method.

This is an excellent collection of papers summarizing the information available in currently active areas of allergy research. It is recommended to all physicians and investigators interested in allergy.

PAUL M. SEEBOHM, M.D.

Police Drugs. By Jean Rolin. Price, $4.75. Pp. 194. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1956.

This is a translation (by Lawrence J. Bendit) of Jean Rolin's impassioned and almost vituperative protest against the use of "police drugs," which term includes all the agents used or misused as "truth serum" equivalents. His ire was aroused by the case of a French policeman from whom an injection of Pentothal brought forth what was presumed to be a confession that later proved to be erroneous, but which in the meanwhile convicted the innocent man of being a collaborationist during the German occupation.

There is a historical account of the various drugs used to elicit "confessions," together with somewhat of an appraisal of their actions. Most of the book deals with the medicolegal and moral aspects of diverting the usual functions of the physician from the realm of diagnosing and treating disease to that of detecting and informing as to criminal matters. As a Frenchman, Rolin makes most of his argument deal with French law and custom. He demonstrates, however, an extraordinary familiarity with both American law and custom. There is an informative chapter on narcoanalysis by Edward V. Saher, which is well done and provides an extensive bibliography.

Admitting the element of bias which may have prompted the book, it is nevertheless a valuable contribution and contains a great deal of information that is not otherwise readily available.

CARL A. DRAGSTEDT, M.D.

Diseases of the Endocrine Glands. Edition 2. By Louis J. Soffer. Price, $16.50. Pp. 1032, with 102 illustrations, 3 color plates, and 28 tables. Lea & Febiger, 600 Washington Sq., Philadelphia 6, 1956.

Dr. Soffer presents the endocrine diseases in a scholarly fashion. The points of differential diagnosis are nicely tabulated, and the prognosis and methods of treatment are given. For those who wish to broaden their understanding there are the sections on histology and embryology of the glands as well as the early historical accounts of the diseases. Research-minded physicians will appreciate the completeness of the bibliography, which includes many papers published during 1955.

The pancreas and diabetes have been omitted from this edition "for two reasons: 1. an effort to maintain the volume within a reasonable length; and 2. the feeling that the field merits separate treatment because of its complexity and detail."

Dr. Sohval's section on the gonads and reproductive physiology maintains the high standards of complete presentation of the clinical syndromes and their management as well as their physiological background and experimental correlations.

The Appendix lists a rather complete set of laboratory tests of endocrine function. These are detailed enough that laboratory technicians could easily learn the procedures, and any physician can quickly determine whether the procedures are done on blood or urine and the quantities and number of samples required.

Short illustrative case histories are included in the sections on differential diagnosis, and a number of nonendocrine diseases are included for the sake of differential exclusion. The book is written in a conversational style; it is remarkably well indexed for ready reference, and the subheadings in bold type are very helpful. This book represents an excellent com-

bination of the clinical, physiological, and biochemical aspects of endocrinology, which makes it a valuable reference book to anyone interested in endocrine diseases.

JAMES T. BRADBURY, SC.D.

Meditations on Medicine and Medical Education: Past and Present. By I. Snapper, M.D. Price, $3.75. Pp. 138. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1956.

This small book of essays on medical history and medical education contains much food for thought. It is written from a background of culture and medical education both wide and deep. Dr. Snapper's medical peregrinations put him in the rank of the peripatetic teachers so renowned in this country 100 years ago—Drake, Gross, Flint, Sims, and others. Snapper's continental training, his Dutch background, and his assimilation of the tradition of Boerhaave provide a background against which modern medicine, Oriental as well as Occidental, are seen in contrast.

There is a fascinating chapter about Dutch medical influences in New York, which was the Dutch colony of New Amsterdam during the early days of the 17th century. The remainder of the book is a sympathetic consideration of Boerhaave, his medical heritage, and his medical progeny as exemplars of bedside teaching. Snapper makes a very sound plea for teachers in medicine in the United States to retain an element of bedside teaching and a healthy respect for the virtues (we already know the limitations) of didactic presentations by clinicians who are filled with wisdom and of ripe years. Certainly in our obsession with the new, in our notion that the accomplishments of science and medicine are magical, it is well to keep in mind the value which still remains in certain elements of didactic teaching. We must not forget that great teachers are still the best audiovisual teaching aids. Altogether this book will be of interest to anyone interested in medicine, in medical teaching, and in medical history. In particular, it would be wholesome reading for those physicians who have forgotten to read anything beyond the latest brochures which rain in torrents across their desks.

WILLIAM B. BEAN, M.D.

Cardiology Notebook for Preliminary Instruction in Medical Curricula. Edited by Alfred P. Fishman, M.D., and others. Price, $2.50. Pp. 97, with illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1955.

Dr. Alfred Fisherman and his colleagues have constructed a "Cardiology Notebook" which is aimed at preliminary instruction in the medical curricula. The notebook contains many important facts. It is beautifuly illustrated, and the format is pleasing. In the section on cardiac fluoroscopy the examination of the heart in the posterior-anterior, left anterior oblique, and right anterior oblique views is beautifully shown by models and x-ray pictures. The text adequately explains the advantages of examination in each of these positions. This is followed by all too few examples which illustrate abnormal findings.

The section on electrocardiography contains tracings of most of the common electrocardiographic abnormalities. There is inadequate information in the text to indicate to the student the criteria for interpretation. Because of this fact the notebook will hardly serve as an electrocardiographic reference book, and it certainly makes no effort to be an introduction to electrocardiography.

This in an experimental book for medical students. I believe the subject matter has been oversimplified in an effort to avoid confusing the budding clinical clerk. For this reason it has limited value.

GEORGE N. BEDELL, M.D.

Hypertension: A Manual for Patients with High Blood Pressure. Edition 2. By Irvine H. Page, A.B., M.D. Price, $3. Pp. 109, with 8 illustrations. Charles C Thomas, Publisher, 201-327 E. Lawrence Ave., Springfield, Ill., 1956.

After many printings and one revision of the first edition of this volume, the second edition has been published. It is a small book, written for the layman interested in information about high blood pressure. It is specifically designed to acquaint the hypertensive patient with various

examinations, his disease, and its treatment. The relationship of atherosclerosis to hypertension is also considered.

Dr. Page's interests and original work in the field of hypertension make him well qualified to discuss the problems of hypertension and to interpret them for patients. His explanations of complex facts and concepts are clear. His discussion of methods of management of hypertension is reasonable and not apt to cause confusion in the minds of patients given different advice. Newer methods of therapy, including the ganglionic blocking agents, are reviewed. Reasonable but not unbridled optimism is the keynote of the section on therapy. Logically, the book concludes with a section on the need for more study in this tremendously complex field.

This book is recommended as a well written, clear, factual volume which can be an adjunct to any modern scheme of therapy for high blood pressure. Dr. Page is to be commended for his attempt to translate this mystery of medicine for the vast audience afflicted and worried by the disease.

WALTER M. KIRKENDALL, M.D.

Collagen Diseases. Volume 2. By John H. Talbott and R. Moleres Ferrandis. Price, $6.50. Pp. 232, with 30 figures and 16 color plates. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1956.

There is much doubt as to whether Klemperer's invention of the term collagen diseases has served a useful purpose or has been an impediment in our understanding of disseminated lupus erythematosus, polyarteritis, dermatomyositis, scleroderma, and thrombotic thrombocytopenic purpura, which Talbott and Ferrandis have included in their monograph entitled "Collagen Diseases." As with many catch phrases or slogans, the words have taken on new meaning. The crux of the matter is very simple. Are the proliferations of collagen, the formation of fibrinoid necrosis, and other changes which characterize the various so-called collagen diseases a result of a multitude of stimuli affecting various tissues but leading to similar results because the reactivity of tissues is limited, or is a single kind of stimulus operating in each of the various disorders whose clinical manifestations and natural history differ from case to case because of the inherent variability of living organisms? There is no answer to this question in this monograph or elsewhere. The value of the book lies rather in the thoughtful discussion of experience accumulated over a long period of time during which these diseases have been under intensive observation by the senior author. I suppose there is no way of escaping the use of letters for diseases in our sense of urgency and haste, but it does make certain pages of the text look like alphabet soup. At best it is distracting and inelegant. A most excellent and detailed bibliography is divided into sections for the separate diseases. There is an index, although not a complete one. These, along with the division of the book into several chapters, facilitate its use in reference work, where it will find its major employment. It is impressive how much and how little steroid hormone therapy has added to our management of these diseases. Even with this form of therapy we have not gained much insight into their nature or mechanisms. This monograph brings out clearly that we are still unable to prevent or treat specifically, rather than by mere palliation, these distressing, disfiguring, and usually fatal disorders.

A number of colored illustrations are included, though unfortunately in some the blues seem to be overdone and the reproduction is far from clear. There are only a few lapses in proof reading. On page xiii there is a comment about persons and institutions who have lent a helping hand, personifying institutions somewhat more than they deserve. X-rays of the chest in the section on disseminated lupus are hard to interpret because of complicating miliary tuberculosis. On page 82, March is spelled March and Marsh. These are minor and trivial errata. The book certainly should be on hand for physicians and dermatologists to use as a reference work, since nowhere else is such material on hand for study in such convenient form. Shortcomings of the book as a definitive treatise mirror shortcomings in our knowledge of these most difficult diseases.

WILLIAM B. BEAN, M.D.

Clinical Management of Renal Failure. By Maurice B. Strauss, M.D., and Lawrence G. Raisz, M.D. Price, $2.75. Pp. 115, with 8 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1956.

Drs. Strauss and Raisz discuss many problems of both acute and chronic renal failure in this monograph. Relatively great emphasis has been placed on the diagnosis and treatment of acute renal failure, while chronic renal failure has been dealt with in more general terms. The nephrotic syndrome is not considered.

The book is written with clarity. Its authors give an excellent summary of their experiences with renal failure and the manner in which they treat this condition. They apparently have had little experience with external dialyzing methods, but despite this (perhaps because), give a very adequate review of methods and critical analysis of published results.

This small volume is recommended as a brief but reasonably complete review of renal failure and its management. It can be used by older physicians as a very pleasant and succinct résumé of recent trends in this area and by younger students of medicine as an introduction to a complex clinical field. The seasoned summary of recent progress in management of these disorders makes this book well worth while.

WALTER M. KIRKENDALL, M.D.

The Story of the Heart Station. By Frank T. Fulton. Privately printed, Providence, R. I.

Every now and then a small book is published which gives a delightful vignette of medical history in the making. This is an account of the heart station at the Rhode Island Hospital in Providence, by Dr. Fulton. He worked with McKenzie, Lewis, Ritchie, and others in the fresh golden days when the electrocardiograph was a monstrous electrical machine, cumbersome and frightening. The patient had to be partially immersed in fluid to get the proper leads. Bewildered practitioners still scoffed at the thought that the laboratory was to bring aid to the practicing physician. This delightful little booklet of reminiscences discusses the circumstances under which one of the very first electrocardiographs was established in a hospital in this country. Everyone interested in cardiology and electrocardiology should read this book, if he can find a copy.

WILLIAM B. BEAN, M.D.

The Office Assistant in Medical or Dental Practice. By Frederick and Towner. Price, $4.75. Pp. 336, with 55 illustrations. Accept 6-21-56 W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

This is one of the most up-to-date books that has been written about the duties of those who work for the physician or dentist and the way in which they should be carried out. It is consistent with the time in its practical presentation of what is expected of the assistant in the modern office and sets up simple duties in a way that makes them efficient office procedures instead of dreaded tasks. After reading this book even the experienced secretary, technician, nurse, or receptionist would be aware of the need for greater organization and planning on her part in handling details so that the doctor can make greater professional use of his time. "The Office Assistant" is specific enough to be a handbook. Instructions are given for such things as sterilization techniques, giving injections, filing, handling the mail, billing, bookkeeping in its application to the doctor's office, appointments, ordering supplies economically, and good telephone techniques. Emphasis is given to the personal qualities of patience, tact, dignity, consideration, discretion, and an interest in human welfare that are basic for the career of office assistant if she is to be able to promote better doctor-patient relationships. Special attention is given to the "Principles of Medical Ethics" that apply to her conduct. This book should inspire every "medical assistant" who reads it to plan for greater efficiency and to be more aware that the career she has chosen is one in which overtime is not to be counted too strictly, as great satisfaction can come from helping others.

MYRETA ESHOM

Studies on Fertility. Including papers read at Conference of Society for Study of Fertility, Birmingham, 1955, being Vol. VII of proceedings of society. Edited by R. G. Harrison. Price, $5. Pp. 156, with 85 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, 24-25 Broad St., Oxford, England, 1955.

This book is the seventh annual volume of the Proceedings of the Society for the Study of Fertility and includes some of the papers read at the Conference of the Society, held in Birmingham, England, during 1955. There is no attempt at synthesis of the publications into an integrated book, each paper dealing with a separate aspect of the problem of fertility. There are fourteen papers; all but one being by British authors, and the papers are evenly divided between those concerning the male and those concerning the female. Five of the articles deal with human fertility and include discussions of cytology of testis biopsies, retrograde ejaculation, postcoital (Huhner) test, and fertility studies in a group of four hundred fifty women following artificial insemination. These papers are all well written and worth reading. The remaining ten articles all deal with experimental animals and present some basic research carried out within the past few years. Subjects include effect of temperature and ischemia on semen and testicular tubules in various animals, rate of flow in the ductus epididymidis, effects of testosterone, reproductive cycle of the cat, fertility in the ewe, and supernumerary spermatozoa in rabbit ova. This latter group of articles has no immediate clinical application, but will be of interest to those doing research in related fields.

This volume may be read with interest by those dealing with problems of fertility, but will be chiefly of value to research workers in anatomy, zoology, and physiology.

GEORGE J. BULKLEY, M.D.

BOOKS RECEIVED

The Lung as a Mirror of Systemic Disease. By Eli H. Rubin, M.D. Price, $12.50. Pp. 288, with 92 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1956.

The Recovery Room: Immediate Postoperative Management. By Max S. Sadove, M.D., and James H. Cross, M.D., with contributions by 24 authorities. Price, $12. Pp. 597, with many illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

The Treatment of Heart Disease: A Clinical Physiologic Approach. By Harry Gross, M.D., and Abraham Jezer, M.D. Price, $13. Pp. 549, with 91 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

VA Medical Monograph: A Follow-up Study of War Neuroses. By Norman Q. Brill, M.D., and Golbert W. Beebe, Ph.D. Price not given. Pp. 393, with 271 tables. Veterans Administration, Department of Medicine and Surgery, Government Printing Office, Washington 25, D. C., 1955.

Blakiston's New Gould Medical Dictionary. Edition 2. Edited by Norman L. Hoerr, M.D., and Arthur Osol, Ph.D., with the cooperation of an editorial board and 88 contributors. Price, $11.50. Pp. 1464, well illustrated. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1956.

The Neurosurgical Alleviation of Parkinsonism. By Irving S. Cooper, M.D., Ph.D. Price, $8.50. Pp. 104, with 68 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1956.

Behringwerk Mitteilungen: Die Schutzimpfung gegen Poliomyelitis. Edited by E. v. Behring. Price, not given. Pp. 291, with few illustrations. Behring Archiv, (16) Marburg/Lahn, Germany, 1956.

Praktische Gastroenterologie. By Dr. Ernst Hafter, with contributions by Priv. Doz. Dr. F. Deucher and Priv. Doz. Dr. H. W. Holz. Price, $11.45; 48 DM. Pp. 380, with 406 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N, 1956.

Handbook of Poisons. By Robert H. Dreisbach. Price, $3. Pp. 428, with no illustrations. Lange Medical Publications, Los Altos, Calif., 1955.

Electrocardiographic Test. Volumes I and II. Edited by Travis Winsor, M.D. Price, $5. Pp. 131 and 159, respectively, with illustrations. The American Heart Association, 44 E. 23d St., New York 10, 1956.

Cryptococcosis: Torulosis or European Blastomycosis. By M. L. Littman, M.D., Ph.D., and Lorenz E. Zimmerman, M.D. Price, $8.50. Pp. 205, with 84 illustrations, 4 pp. color plates, and 11 tables. Grune & Stratton, Inc., 381 Fourth Ave., New York 16; 99 Russell St., London, W. C. 1, 1956.

Die zentralnervolse Regulation des Blutbildes. By Prof. Etsuzo Komiya. Price, $2.85; 12 DM. Pp. 72, with 49 illustrations and 7 tables. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N; Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16, 1956.

The Drug Addict as a Patient. By Marie Nyswander, M.D. Price, $4.50. Pp. 179, with no illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16; 99 Great Russell St., London, W. C. 1, 1956.

Diagnosis and Treatment of Peripheral Vascular Disorders. By David I. Abramson, M.D., F. A. C. P. Price, $13.50. Pp. 537, with 82 illustrations and 18 tables. Paul B. Hoeber, Inc., 49 E. 33d St., New York 16, 1956.

Klinische Funktionsdiagnostik. By Doz. Dr. H. Küchmeister, with contributions by Prof. Dr. W. Bolt, Prof. D. H. Goldbeck, and Dr. H. Hamm. Price, $11; 49.50 DM. Pp. 411, with 152 illustrations and 52 tables. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N; Intercontinental Medical Book Corp., 381 Fourth Ave., New York 16, 1956.

Polysaccharides in Biology: Transactions of the First Conference April 27, 28, and 29, 1955. Edited by Georg F. Springer. Price, $5. Pp. 271, with 31 illustrations and 21 tables. Josiah Macy, Jr. Foundation Publications, 16 W. 46th St., New York 36, 1956.

Neuropharmacology: Transactions of the Second Conference May 25, 26, and 27, 1955. Edited by Harold A. Abramson, M.D. Price, $4.25. Pp. 328, with 85 illustrations and 26 tables. Josiah Macy, Jr. Foundation Publications, 16 W. 46th St., New York 36, 1956.

News and Comment

ANNOUNCEMENTS

Health Research Facilities Program.—On July 30, 1956, the President signed the Health Research Facilities Act of 1956, which authorizes the appropriation of funds not to exceed $30 million for each of three years to assist in the financing of the construction of facilities for research in the "sciences related to health." The Act defines "sciences related to health" as including medicine, osteopathy, dentistry, and public health, and fundamental and applied sciences when related thereto. The assistance is to be in the form of grants in aid to public and nonprofit institutions on a basis of not more than 50% for the Federal share. Items not creditable for matching purposes include (1) costs for the acquisition of land or off-site improvements and (2) obligations made prior to the award of the research facilities grant concerned. The Congress has now appropriated $30 million to the Public Health Service, Department of Health, Education and Welfare, for this program. These funds are now available and will remain available until expended.

The funds are to be used to provide additional research facilities through the construction and/or equipping of new buildings or the expansion, remodeling, alteration, and/or equipping of existing buildings.

The new law provides for the appointment of a National Advisory Council on Health Research Facilities. It is expected that this Council will meet in the near future to establish policies and approve regulations for the administration of the new program. The Surgeon General is not permitted to award a research facilities grant in aid which has not previously been approved by the Council.

Application forms, as well as additional information, will be supplied promptly upon request to the Division of Research Grants, National Institutes of Health, Public Health Service, Bethesda 14, Md.

Senior Research Fellowship Program.—A Senior Research Fellowship program, administered by the National Institutes of Health, Public Health Service, is now in operation. During the first year, this program will provide for a total of 40 to 50 awards to the nation's medical schools, dental schools, and schools of public health. These awards will be increased by a like number each year for five years until a total of 200 to 250 such fellowships are awarded annually.

The awards will be for a maximum of $10,000 a year and may be retained for as long as five years. Only three applications may be made per year by each school. The program is designed to attract and hold able investigators in the preclinical sciences.

Requests for information concerning this program should be addressed to the Chief, Research Fellowship Program, Division of Research Grants, National Institutes of Health, Bethesda 14, Md.

American College of Physicians Receives Research Grant.—A research grant of $43,100 has been awarded the American College of Physicians for the period Sept. 1, 1956, through Aug. 31, 1957, by the Department of Health, Education, and Welfare of the Public Health Service in furtherance of its project to evaluate internal medicine in hospitals. This project, "to establish a minimal standard of quality and efficiency of the practice of internal medicine in hospitals," was initiated in early 1956, by the College's Committee on Criteria for Hospital Accreditation, under the chairmanship of Dr. Arthur R. Colwell, Sr., F. A. C. P., Chicago.

The Director of the study is Dr. Marion A. Blankenhorn, F. A. C. P., Cincinnati, who is devoting his full time to the project. A pilot study of approximately 100 representative hospitals is being conducted by observing practice methods with particular reference to internal medicine. Twenty or more mature and responsible physicians are being sent to selected sites to observe current practices; to record the type of patient admitted to a hospital, the diseases, length of stay, and the means employed for diagnosis and treatment; and to classify findings—namely, approved, provisionally approved, and not approved. A search is being directed to the mechanics of internal medicine as practiced in a wide variety of circumstances (large, small, voluntary, tax-supported, private, teaching, or nonteaching), especially the use of clinical

laboratory devices; habits of consultation, and use of ancillary skills, such as physical medicine, rehabilitation, and preventive medicine. Such observations and records will be edited by the Director and reviewed by the Committee on Criteria.

Whereas appraisal of medical care will be the primary objective, information will be gathered also regarding internships and residencies in Medicine where such programs exist. Close liaison will be maintained with the Council on Medical Education and Hospitals of the American Medical Association and appropriate committees in the Association of American Medical Colleges. The Committee does not suggest that this pilot study shall substitute for any part of the present programs of the Joint Commission on Accreditation of Hospitals or the Council on Medical Education and Hospitals of the American Medical Association, but it will proceed parallel to the existing programs of both, probably leading to some revision in their Internal Medicine policies in the future.

Course in Electrocardiology.—A course in practical electrocardiology will be presented Dec. 3-7, 1956, in Houston, Texas, by Dr. Demetrio Sodi-Pallares, Chief of the Department of Electrocardiology at the National Institute of Cardiology, Mexico, D. F., under auspices of The University of Texas Postgraduate School of Medicine and Baylor University College of Medicine.

In addition to Dr. Sodi-Pallares' evening course and his clinical-pathological conference discussions, individual instruction in reading electrocardiograms will be provided by faculty members of the sponsoring institutions. For more advanced students, panel discussions will be held on subjects of special interest to electrocardiologists. Inquiries should be addressed to The University of Texas Postgraduate School of Medicine, Texas Medical Center, Houston 25, Texas.

National Foundation for Infantile Paralysis Announces Postdoctoral Fellowships.—The National Foundation for Infantile Paralysis announces that postdoctoral fellowships are available for full-time study in preparation for careers in research and/or academic medicine, or in the clinical fields of psychiatry; rehabilitation; orthopedics; the management of poliomyelitis and preventive medicine.

Financial support of the Fellow varies as stipulated below, and compensation to the institution is arranged according to the program undertaken. For a full academic program, tuition and fees are paid; for other programs, a sum not to exceed $1250 per year, including tuition.

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Applications	March 1		May
must be	Sept. 1	for consideration in	November
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Specifically, fellowships are offered:

I. For postdoctoral training in research and/or academic medicine. Awarded to applicants with an M.D. or Ph.D. or equivalent degree for basic or advanced training in laboratory research in medicine and the related biological and physical sciences. This program is not intended for experienced investigators who need support for a research project.

Financial benefits, in addition to the compensation to the institution, vary from $3600 to $6000 a year. Under unusual circumstances, higher stipends may be permitted. Transportation not to exceed $600 may be paid if foreign study is approved.

II. For postdoctoral study in the clinical fields of:

A. *REHABILITATION:*

(1) For licensed physicians interested in rehabilitation as it relates to their specialty and who wish to study the concept and basic techniques of rehabilitation. One year of internship is required and license to practice in the United States.

(2) For physicians who wish specialty training in Physical Medicine and Rehabilitation. Awards are made for a period of one, two, or three years,

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depending upon the time required to complete eligibility requirements for certification by the American Board of Physical Medicine and Rehabilitation. Preference is given to applicants under 40 years of age.

B. THE MANAGEMENT OF POLIOMYELITIS:

For licensed physicians who wish to acquire a knowledge of the various aspects of the total care of poliomyelitis patients. A fellowship for one year for full-time study may be undertaken at any institution having suitable facilities and staff for this type of program. One year of internship is required.

Financial benefits are $300 or $350 per month, depending on marital status, with $25 additional for each dependent child. Compensation to the institution is also arranged.

C. PSYCHIATRY:

For licensed physicians who have had two years of graduate training acceptable to the American Board of Psychiatry and Neurology and who are interested in the emotional problems of patients with physical disabilities. The program of study is to be undertaken in a setting where medical and associate medical personnel are engaged cooperatively in a program of comprehensive patient care. Interest in research and teaching is highly desirable. Awards are made for a period of one year and are subject to renewal.

Financial benefits, in addition to the compensation to the institution, vary from $3600 to $6000 a year. Under unusual circumstances, higher stipends may be permitted.

D. ORTHOPEDICS:

For surgeons who have completed requirements for certification by the American Board of Orthopedic Surgery (or who have had equivalent training) and who are interested in teaching or research in orthopedics. The age limit is 36. Awards are made for a period of one year and are subject to renewal.

Financial benefits, in addition to the compensation to the institution, vary from $4500 to $6000. Under unusual circumstances, higher stipends may be permitted.

E. PREVENTIVE MEDICINE:

For physicians who desire to prepare for the teaching of preventive medicine. Applicants must have had two years of training and experience, including responsibility for teaching, in one of the areas related to preventive medicine. Awards are made for a period of one year and are subject to renewal.

Financial benefits, in addition to the compensation to the institution, vary from $4500 to $6000. Under unusual circumstances, higher stipends may be permitted.

III. For medical students: Two- to three-month fellowships are available for medical students who wish to take advantage of vacation time for study in research, public health and preventive medicine, or rehabilitation. This program is administered by the National Foundation through the deans of the approved medical schools, to whom inquiries should be addressed.

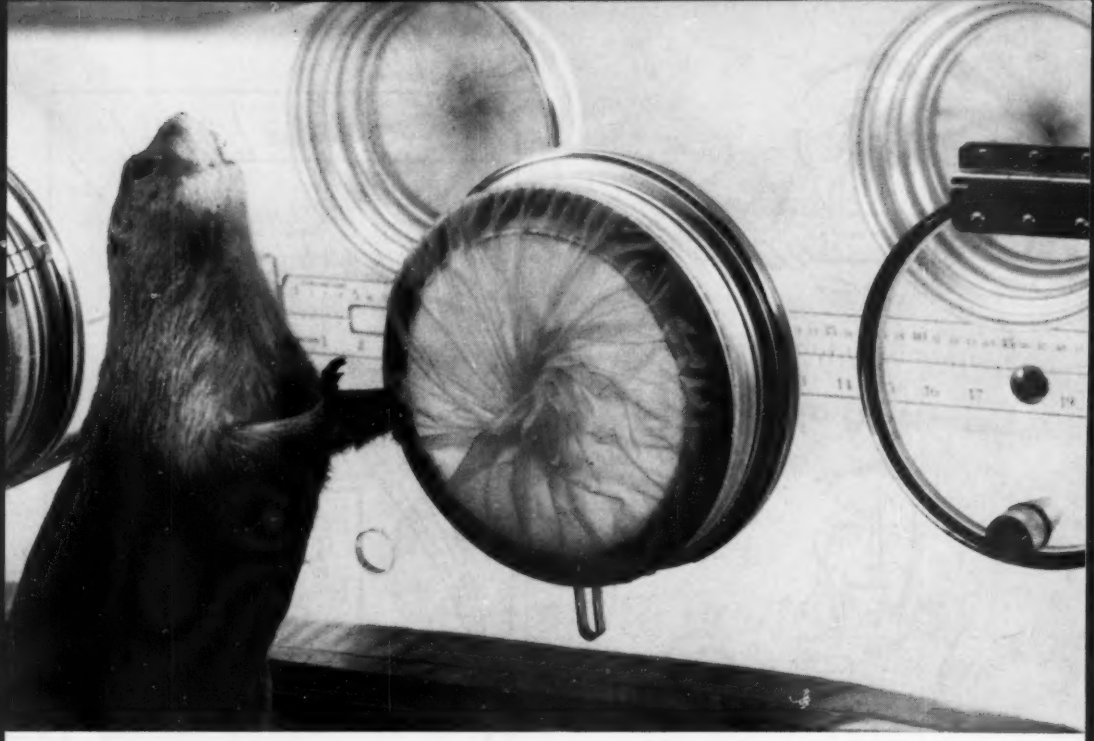
IV. For students in the medical associate fields: for physical therapists to prepare for teaching; for health educators from State Health and Education Departments to study in an approved school of Public Health, and for social scientists to apply their professional skills to the emotional problems of patients with physical disabilities.

Also scholarships are awarded for the basic professional education of medical social workers and physical therapists.

The National Foundation has authorized the expenditure of $23,500,000 since 1938 for scholarships and fellowships, and for aid to educational institutions, professional organizations, and related activities.

For further information write to:

Division of Professional Education
National Foundation for Infantile Paralysis
120 Broadway
New York 5, N. Y.



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Complete literature available on request.

References: 1. Hisaw, F. L.: Physiol. Zoöl. *2*:59 (Jan.) 1929. 2. Hisaw, F. L.; Meyer, R. K., and Fevold, H. L.: Proc. Soc. Exper. Biol. & Med. *27*:400 (Feb.) 1930. 3. Hisaw, F. L., and Zarrow, M. X.: Vitamins & Hormones *8*:151, 1951. 4. Perkoff, G. T., *et al.*: J. Clin. Endocrinol. & Metab. *14*:531 (May) 1954. 5. Abramson, D., and Reid, D. E.: J. Clin. Endocrinol. & Metab. *15*:206 (Jan.) 1955. 6. Eichner, E.; Waltner, C.; Goodman, M., and Post, S.: Am. J. Obst. & Gynec. *71*:1035 (May) 1956.

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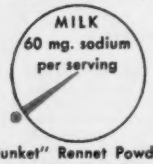

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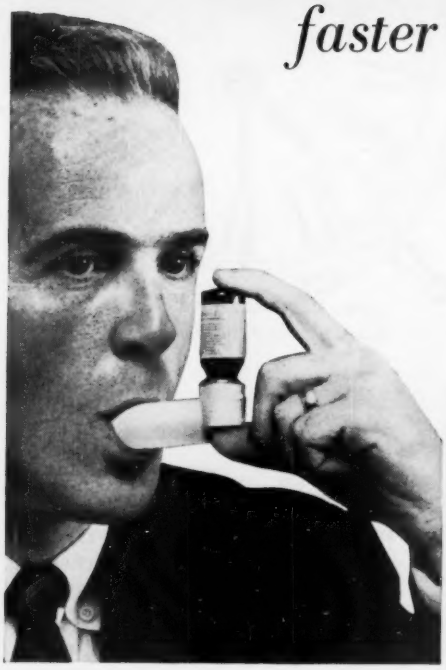

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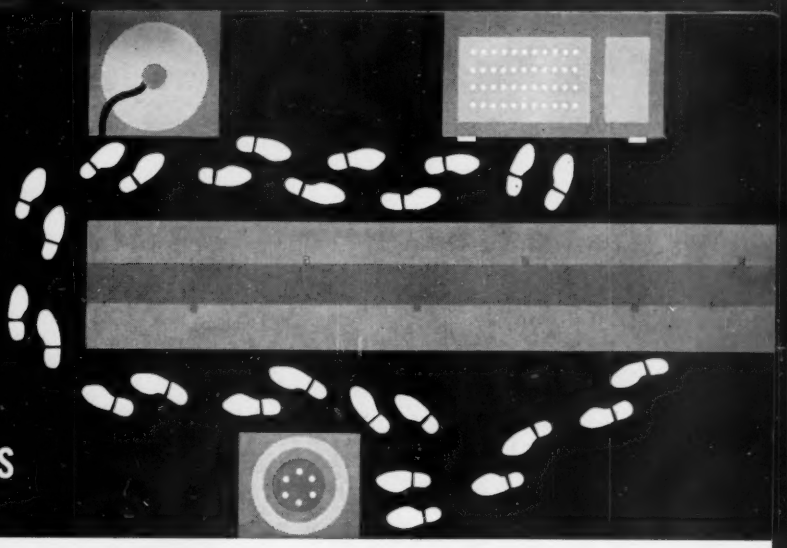

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1. Silverman, M.: J. Ment. Sc. *101*:640 (July) 1955.

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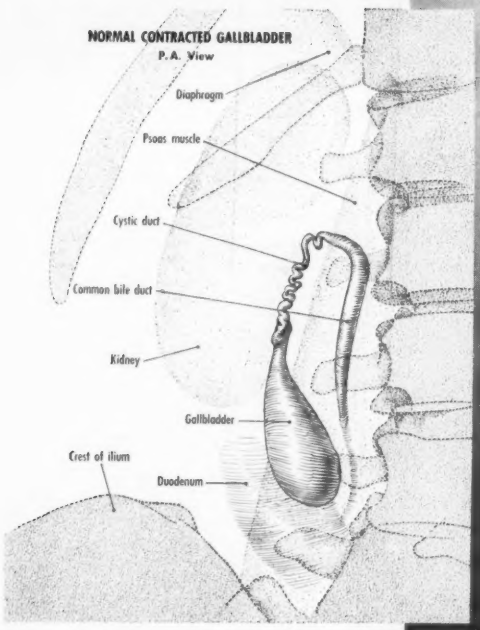

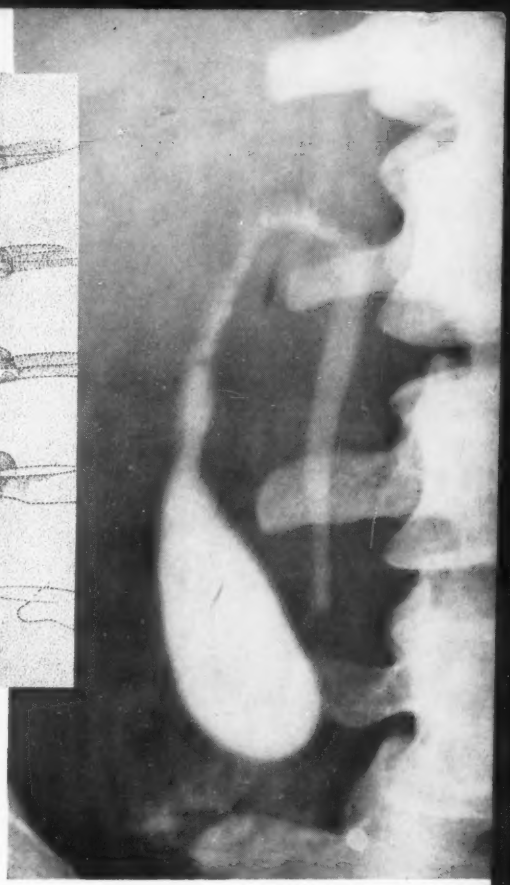

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Buckstein, Jacob: The Digestive Tract in Roentgenology. Philadelphia, J. B. Lippincott Co., 2nd ed., 1953, vol. 2, p. 1003.

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Friedgood, C.E., and Ripstein, C.B.: Chlorpromazine ('Thorazine') in the Treatment of Intractable Hiccups, J.A.M.A. *157*:309 (Jan. 22) 1955.

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